

Derivatives of 2-arylimino-2,3-dihydrothiazoles, their preparation processes and their therapeutic use

A subject of the present Application is new derivatives of 2-arylimino-2,3-dihydrothiazoles and their preparation processes. These products have a good affinity with certain sub-types of somatostatin receptors and therefore have useful pharmacological properties. The invention also relates to these same products as  
5 medicaments, the pharmaceutical compositions containing them and their use for the preparation of a medicament intended to treat pathological states or diseases in which one (or more) somatostatin receptors are involved.

Somatostatin (SST) is a cyclic tetradecapeptide which was isolated for the first time from the hypothalamus as a substance which inhibits the growth hormone (Brazeau P.  
10 et al., *Science* 1973, 179, 77-79). It also operates as a neurotransmitter in the brain (Reisine T. et al., *Neuroscience* 1995, 67, 777-790; Reisine T. et al., *Endocrinology* 1995, 16, 427-442). Molecular cloning has allowed it to be shown that the bioactivity of somatostatin depends directly on a family of five receptors linked to the membrane.

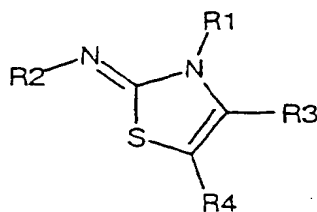
The heterogeneity of the biological functions of somatostatin has led to studies which  
15 try to identify the structure-activity relationships of peptide analogues on somatostatin receptors, which has led to the discovery of 5 sub-types of receptors (Yamada et al., *Proc. Natl. Acad. Sci. U.S.A.*, 89, 251-255, 1992; Raynor, K. et al, *Mol. Pharmacol.*, 44, 385-392, 1993). The functional roles of these receptors are currently being actively studied. The affinities with different sub-types of somatostatin receptors have been  
20 associated with the treatment of the following disorders/diseases. Activation of sub-types 2 and 5 has been associated with suppression of the growth hormone (GH) and more particularly with that of adenomas secreting GH (acromegalia) and those secreting hormone TSH. Activation of sub-type 2 but not sub-type 5 has been associated with the treatment of adenomas secreting prolactin. Other indications associated with the  
25 activation of sub-types of somatostatin receptors are the recurrence of stenosis, inhibition of the secretion of insulin and/or of glucagon and in particular diabetes mellitus, hyperlipidemia, insensibility to insulin, Syndrome X, angiopathy, proliferative retinopathy, dawn phenomenon and nephropathy; inhibition of the secretion of gastric

acid and in particular peptic ulcers, enterocutaneous and pancreaticocutaneous fistulae, irritable colon syndrome, dumping syndrome, aqueous diarrhoea syndrome, diarrhoea associated with AIDS, diarrhoea induced by chemotherapy, acute or chronic pancreatitis and secretory gastrointestinal tumours; the treatment of cancer such as hepatomas; the inhibition of angiogenesis, the treatment of inflammatory disorders such as arthritis; chronic rejection of allografts; angioplasty; the prevention of bleeding of grafted vessels and gastrointestinal bleeding. The agonists of somatostatin can also be used to reduce the weight of a patient.

Among the pathological disorders associated with somatostatin (Moreau J.P. et al., Life Sciences 1987, 40, 419; Harris A.G. et al., *The European Journal of Medicine*, 1993, 2, 97-105), there can be mentioned for example: acromegalia, hypophyseal adenomas, Cushing's disease, gonadotrophinomas and prolactinomas, catabolic side-effects of glucocorticoids, insulin dependent diabetes, diabetic retinopathy, diabetic nephropathy, hyperthyroidism, gigantism, endocrine gastroenteropancreatic tumours including carcinoid syndrome, VIPoma, insulinoma, nesidioblastoma, hyperinsulinemia, glucagonoma, gastrinoma and Zollinger-Ellison's syndrome, GRFoma as well as acute bleeding of oesophageal veins, gastroesophageal reflux, gastroduodenal reflux, pancreatitis, enterocutaneous and pancreatic fistulae but also diarrhoea, refractory diarrhoea of acquired immune deficiency syndrome, chronic secretory diarrhoea, diarrhoea associated with irritable bowel syndrome, disorders linked with gastrin releasing peptide, secondary pathologies with intestinal grafts, portal hypertension as well as haemorrhages of the veins in patients with cirrhosis, gastro-intestinal haemorrhage, haemorrhage of the gastroduodenal ulcer, Crohn's disease, systemic sclerosis, dumping syndrome, small intestine syndrome, hypotension, scleroderma and medullar thyroid carcinoma, illnesses linked with cell hyperproliferation such as cancers and more particularly breast cancer, prostate cancer, thyroid cancer as well as pancreatic cancer and colorectal cancer, fibroses and more particularly fibrosis of the kidney, fibrosis of the liver, fibrosis of the lung, fibrosis of the skin, also fibrosis of the central nervous system as well as that of the nose and fibrosis induced by chemotherapy, and other therapeutic fields such as, for example, cephalas including cephalas associated with hypophyseal tumours, pain, panic attacks, chemotherapy, cicatrization of wounds, renal insufficiency resulting from delayed development, obesity and delayed development linked with obesity, delayed uterine development, dysplasia of the skeleton, Noonan's syndrome, sleep apnea syndrome, Graves' disease, polycystic disease of the ovaries, pancreatic pseudocysts and ascites, leukemia, meningioma, cancerous cachexia, inhibition of H pylori, psoriasis, as well as Alzheimer's disease. Osteoporosis can also be mentioned.

The Applicant found that the compounds of general formula (I) described hereafter have an affinity and a selectivity for the somatostatin receptors. As somatostatin and its peptide analogues often have a poor bioavailability by oral route and a low selectivity (Robinson, C., Drugs of the Future, 1994, 19, 992; Reubi, J.C. et al., TIPS, 1995; 16, 110), said compounds, non-peptide agonists or antagonists of somatostatin, can be advantageously used to treat pathological states or illnesses as presented above and in which one (or more) somatostatin receptors are involved. Preferably, said compounds can be used for the treatment of acromegalia, hypophyseal adenomas or endocrine gastroenteropancreatic tumours including carcinoid syndrome.

10 The compounds of the present invention correspond to general formula (I)

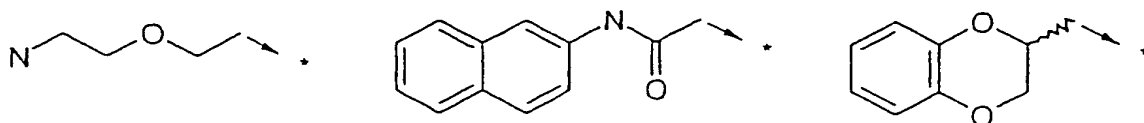


(I)

in racemic, enantiomeric form or all combinations of these forms, in which:

R1 represents an amino(C<sub>2</sub>-C<sub>7</sub>)alkyl, aminoalkylarylalkyl, aminoalkylcycloalkylalkyl, (C<sub>1</sub>-C<sub>15</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkylalkyl, cyclohexenylalkyl, alkenyl, alkynyl, carbocyclic aryl radical containing at least two rings of which at least one is not aromatic, carbocyclic or heterocyclic aralkyl radical optionally substituted on the aryl group, bis-arylalkyl, alkoxyalkyl, furannylalkyl or tetrahydrofurannylalkyl, dialkylaminoalkyl, N-acetoamidoalkyl, cyanoalkyl, alkylthioalkyl, arylhydroxyalkyl, aralkoxyalkyl, morpholinoalkyl, pyrrolidinoalkyl, piperidinoalkyl, N-alkylpyrrolidinoalkyl, N-alkylpiperazinylalkyl or oxypyrrolidinoalkyl radical,

or R1 represents one of the radicals represented below:

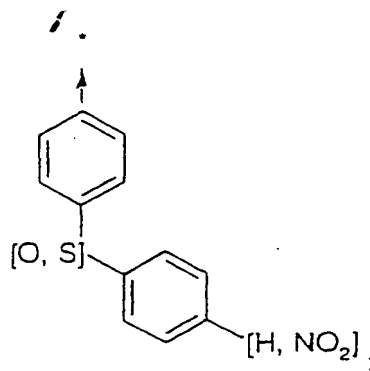
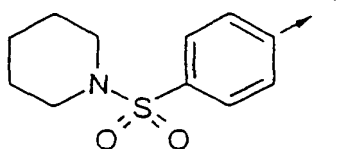


or also R1 represents a -C(R11)(R12)-CO-R10 radical;

R2 represents an optionally substituted carbocyclic or heterocyclic aryl radical,

or R2 represents one of the radicals represented below:

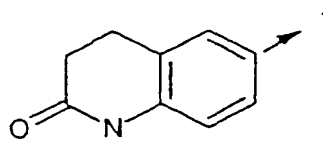
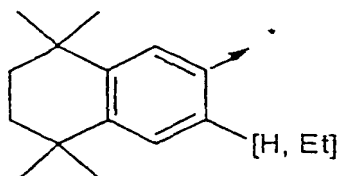
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10 R3 represents an alkyl, adamantyl, optionally substituted carbocyclic or heterocyclic aryl radical, carbocyclic or heterocyclic aralkyl optionally substituted on the aryl group,

or R3 represents one of the radicals represented below:

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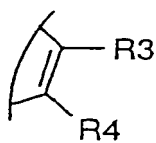
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or also R3 represents a -CO-R5 radical;

R4 represents H, alkyl, carbocyclic or heterocyclic aralkyl optionally situated on the aryl radical;

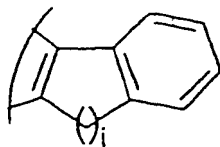
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or then the



radical represents a radical of general formula

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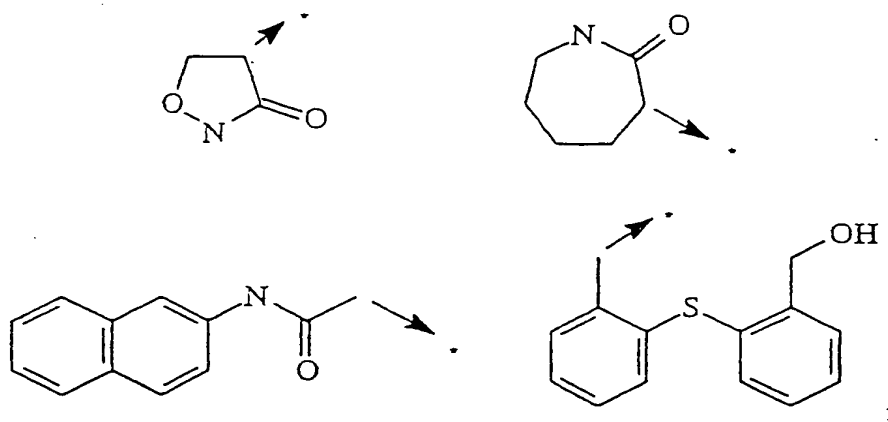
in which i represents an integer from 1 to 3;

35 R5 represents the N(R6)(R7) radical;



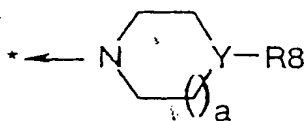
R6 represents a (C<sub>1</sub>-C<sub>16</sub>)alkyl, cycloalkylalkyl, hydroxyalkyl, aryloxyalkyl radical, carbocyclic or heterocyclic aralkyl radical optionally substituted on the aryl group, aralkoxyalkyl, arylhydroxyalkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, cyclohexenyl, cyclohexenylalkyl, alkylthiohydroxyalkyl, cyanoalkyl, N-acetamidoalkyl radical, bis-arylalkyl radical optionally substituted on the aryl groups, di-arylalkyl radical optionally substituted on the aryl groups, morpholinoalkyl, pyrrolidinoalkyl, piperidinoalkyl, N-alkylpyrrolidinoalkyl, oxopyrrolidinoalkyl, tetrahydrofuranylalkyl, N-benzylpyrrolidinoalkyl, N-alkylpiperazinylalkyl, N-benzylpiperazinylalkyl, N-benzylpiperidinylalkyl or N-alkoxycarbonylpiperidinyl radical, or R6 represents a (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl radical optionally substituted by a radical chosen from the group comprising the hydroxy radical and an alkyl radical,

or R6 represents one of the radicals represented below:



R7 represents H or an alkyl, hydroxyalkyl, mono- or di-aminoalkyl or aralkyl radical;

or the -N(R6)(R7) radical represents the radical of the following general formula:



15 in which:

R8 represents H, alkyl, hydroxyalkyl, optionally substituted carbocyclic or heterocyclic aryl, aralkyl optionally substituted on the aryl group, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, bis-arylalkyl, piperidinyl, pyrrolidinyl, hydroxy, arylalkenyl,

or R8 represents -X-(CH<sub>2</sub>)<sub>b</sub>-R9;

R9 represents H or an alkyl, alkoxy, aryloxy, optionally substituted carbocyclic or heterocyclic aryl, morpholinyl, pyrrolidinyl, alkylamino or N,N'-(alkyl)(aryl)amino radical;

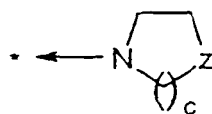
X represents CO, CO-NH or SO<sub>2</sub>;

5 Y represents CH or N;

a represents 1 or 2;

b represents an integer from 0 to 6;

or the N(R6)(R7) radical represents a radical of general formula

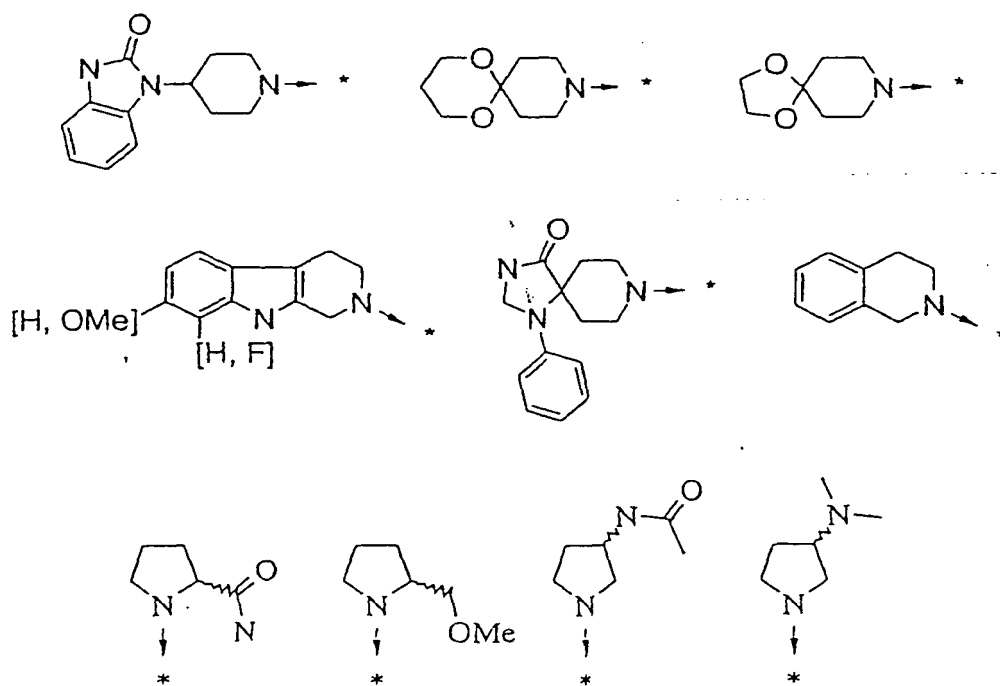


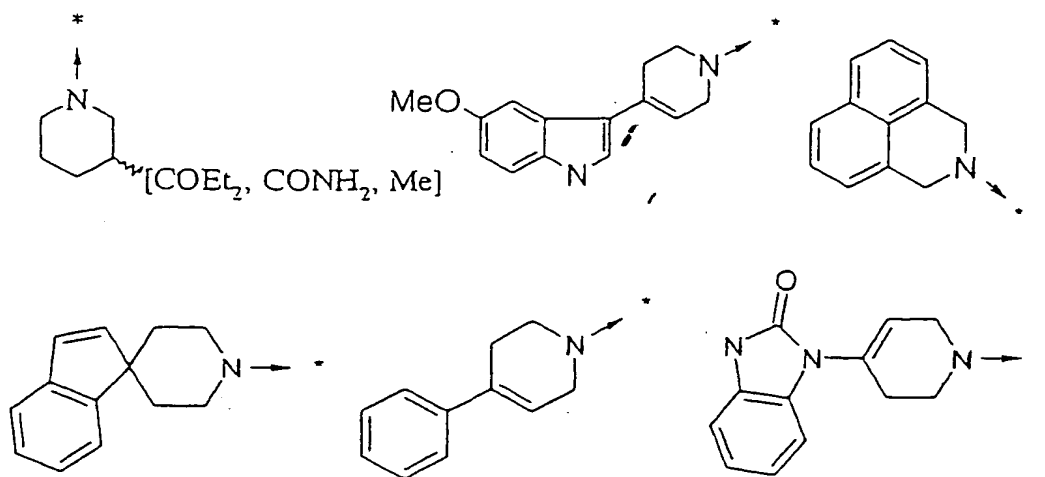
in which:

10 Z represents CH, O or S;

c represents an integer from 0 to 4;

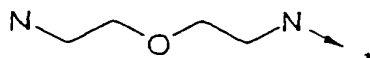
or the N(R6)(R7) radical represents one of the radicals represented below:





R10 represents an amino(C<sub>2</sub>-C<sub>7</sub>)alkylamino, ((aminoalkyl)aryl)alkylamino, ((aminoalkyl)cycloalkyl)alkylamino, piperazinyl, homopiperazinyl radical,

or R10 represents the radical represented below:



R11 represents H;

R12 represents H or an alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, optionally substituted carbocyclic or heterocyclic aralkyl, propargyl, allyl, hydroxyalkyl, alkylthioalkyl, arylalkylalkoxyalkyl, arylalkylthioalkoxyalkyl radical;

or the compounds of the invention are salts of the compounds of general formula (I).

When the compounds of general formula (I) contain the R1, R2, R3, R4, R6, R8, R9 or R12 radicals including a substituted aryl radical or an aralkyl substituted on the aryl group, said aryl or aralkyl radicals are preferably such that:

- For R1, when the aryl group is substituted, it can be from 1 to 5 times (other than the bond which links it with the remainder of the molecule) by radicals chosen independently from the group comprising a halogen atom and an alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, aryl, aralkoxy or SO<sub>2</sub>NH<sub>2</sub> radical. Two substituents can, if appropriate, be linked together and form a ring, for example by representing together a methylenedioxy or propylene radical.

- For R2, when the aryl group is substituted, it can be from 1 to 5 times (other than the bond which links it with the remainder of the molecule). The aryl radical can be

substituted by radicals chosen independently from the group comprising a halogen atom and an alkyl, alkoxy, alkylthio, haloalkyl, alkenyl, haloalkoxy, nitro, cyano, azido, SO<sub>2</sub>N, mono- or di-alkylamino, aminoalkyl, aralkoxy, or aryl radical. Two substituents can, if appropriate, be linked together and form a ring, for example by representing  
5 together a methylenedioxy, ethylenedioxy or propylene radical.

- For R3, when the aryl group or groups (originating from an aryl or aralkyl radical) are substituted, they can be, according to the case, from 1 to 5 times (other than the bond which links them with the remainder of the molecule). The carbocyclic aryl or aralkyl radicals can be substituted from 1 to 5 times on the aryl ring by radicals chosen  
10 independently from the group comprising a halogen atom and an alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, cyano, azido, mono- or di-alkylamino, pyrrolidinyl, morpholinyl, aralkoxy or aryl radical. Two substituents can, if appropriate, be linked together and form a ring, for example by representing together an alkylenedioxy radical containing 1 to 3 carbon atoms. The heterocyclic aryl or aralkyl  
15 radicals of R3 can be substituted 1 to 2 times on the ring by radicals chosen independently from the group comprising a halogen atom and an alkyl radical.

- For R4, when the aryl group is substituted, it can be from 1 to 5 times (other than the bond which links it with the remainder of the molecule). The aryl radical can be substituted by the radicals chosen independently from the group comprising a halogen  
20 atom and an alkyl or alkoxy radical.

- For R6, when the aryl group or groups are substituted, they can be from 1 to 5 times (other than the bond which links them with the remainder of the molecule). The optional substituents on the aryl groups are chosen independently from the group comprising a halogen atom and an alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, aryl,  
25 aryloxy or SO<sub>2</sub>NH<sub>2</sub> radical.

- For R8, when the aryl group or groups are substituted, they can be from 1 to 5 times (other than the bond which links them with the remainder of the molecule). The optional substituents on the aryl groups are chosen independently from the group comprising a halogen atom and an alkyl, haloalkyl, alkoxy, hydroxy, cyano, nitro or  
30 alkylthio radical.

- For R9, when the carbocyclic or heterocyclic aryl radical is substituted, it can be from 1 to 5 times (other than the bond which links it with the remainder of the molecule). The optional substituents on the aryl group are chosen independently from the group comprising a halogen atom and an alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio,  
35 carbocyclic aryl, hydroxy, cyano or nitro radical.

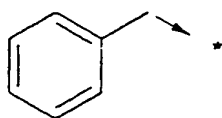
- For R12, when the carbocyclic or heterocyclic aryl radical is substituted, it can be from 1 to 5 times (other than the bond which links it with the remainder of the molecule). The optional substituents on the aryl group are chosen independently from the group comprising a halogen atom and an alkyl, alkoxy, carbocyclic aryl, aralkoxy, hydroxy, cyano or nitro radical.

By alkyl, unless specified otherwise, is meant a linear or branched alkyl radical containing 1 to 6 carbon atoms. By cycloalkyl, unless specified otherwise, is meant a monocyclic carbon system containing 3 to 7 carbon atoms. By alkenyl, unless specified otherwise, is meant a linear or branched alkyl radical containing 1 to 6 carbon atoms and having at least one unsaturation (double bond). By alkynyl, unless specified otherwise, is meant a linear or branched alkyl radical containing 1 to 6 carbon atoms and having at least one double unsaturation (triple bond). By carbocyclic or heterocyclic aryl, is meant a carbocyclic or heterocyclic system containing at least one aromatic ring, a system being referred to as heterocyclic when at least one of the rings which comprise it contains a heteroatom (O, N or S). By haloalkyl, is meant an alkyl radical of which at least one of the hydrogen atoms (and optionally all) is replaced by a halogen atom.

By alkylthio, alkoxy, haloalkyl, haloalkoxy, aminoalkyl, alkenyl, alkynyl and aralkyl radicals, is meant respectively the alkylthio, alkoxy, haloalkyl, haloalkoxy, aminoalkyl, alkenyl, alkynyl and aralkyl radicals the alkyl radical of which has the meaning indicated previously.

By linear or branched alkyl having 1 to 6 carbon atoms, is meant in particular the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, pentyl, neopentyl, isopentyl, hexyl, isohexyl radicals. By cycloalkyl, is meant in particular the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl radicals. By carbocyclic or heterocyclic aryl, is meant, in particular the phenyl, naphthyl, pyridinyl, furanyl, thiophenyl, indanyl, indolyl, imidazolyl, benzofuranyl, benzothiophenyl, phthalimidyl radicals. By carbocyclic or heterocyclic aralkyl, is meant in particular the benzyl, phenylethyl, phenylpropyl, phenylbutyl, indolylalkyl, phthalimidoalkyl, naphthylalkyl, furanylalkyl, thiophenylalkyl, benzothiophenylalkyl, pyridinylalkyl and imidazolylalkyl radicals.

When an arrow emanates from a chemical structure, said arrow indicates the point of attachment. For example :



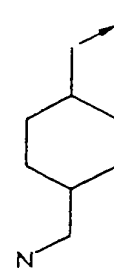
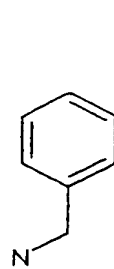
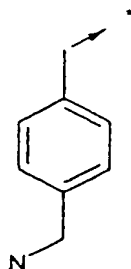
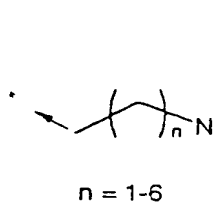
represents the benzyl radical.

Preferably, the compounds of general formula (I) are such that:

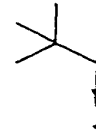
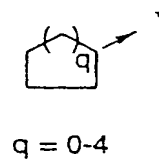
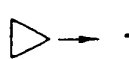
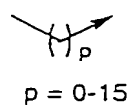
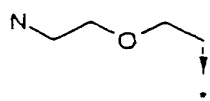
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R1 represents -C(R11)(R12)-CO-R10 or one of the following radicals:

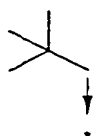
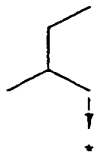
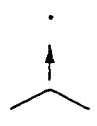
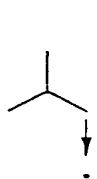
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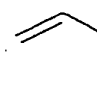
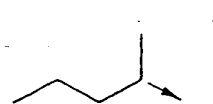
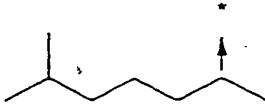
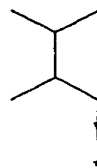
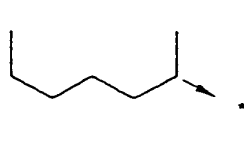
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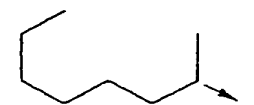
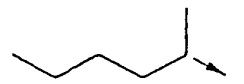
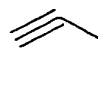
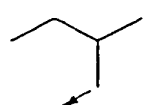
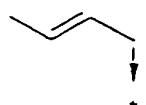
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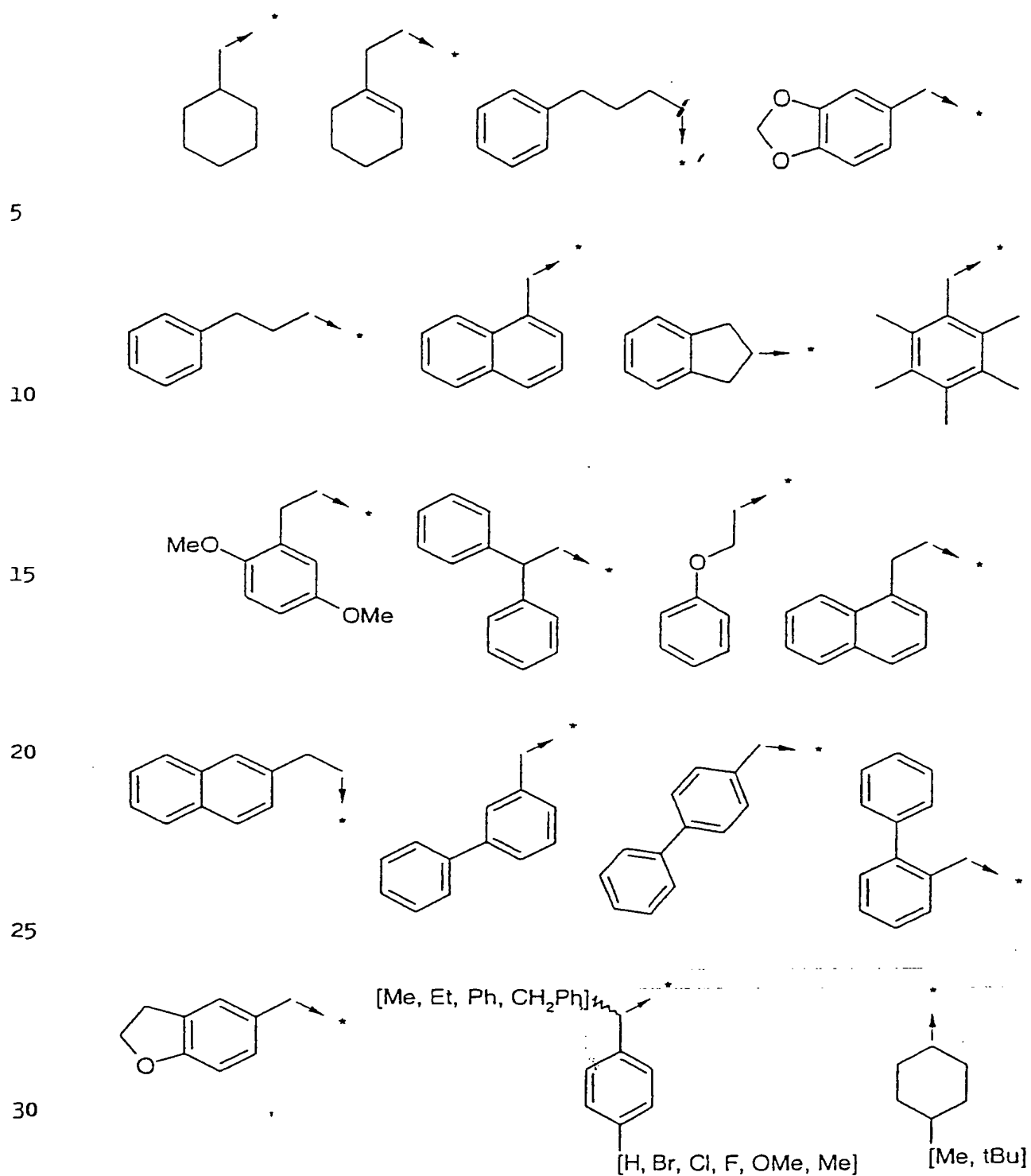
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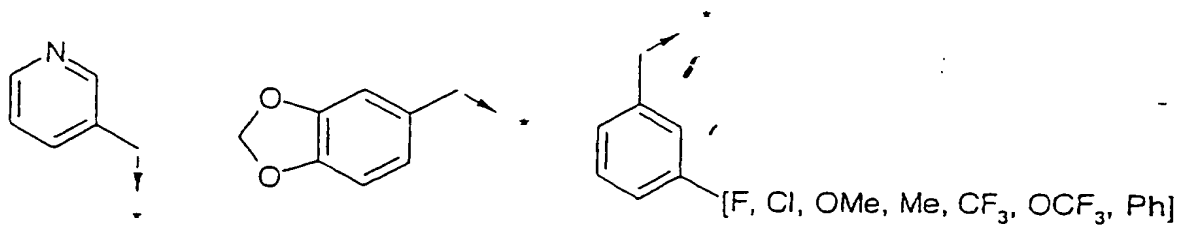


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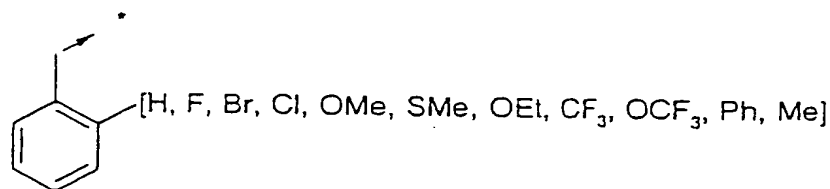


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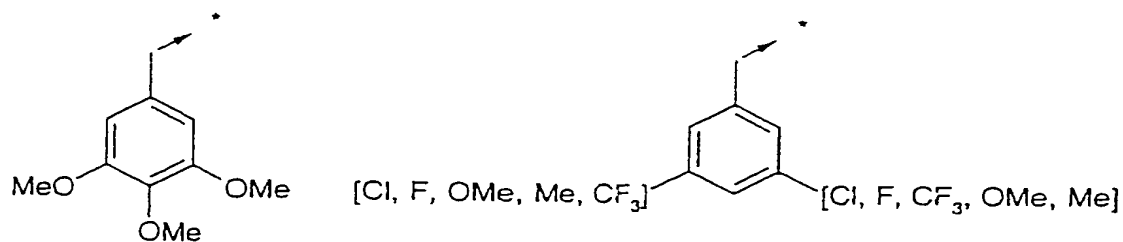




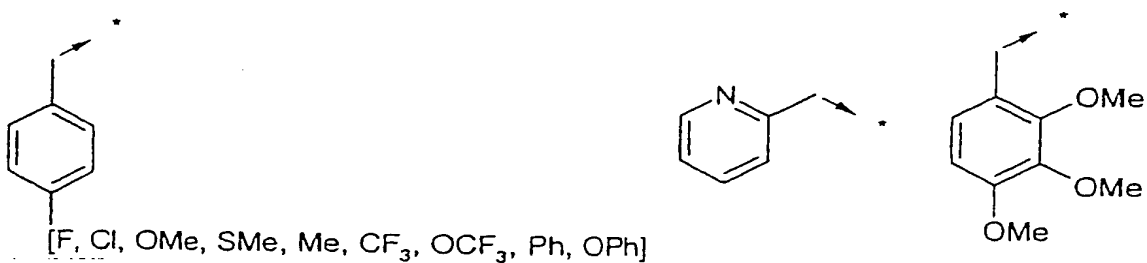
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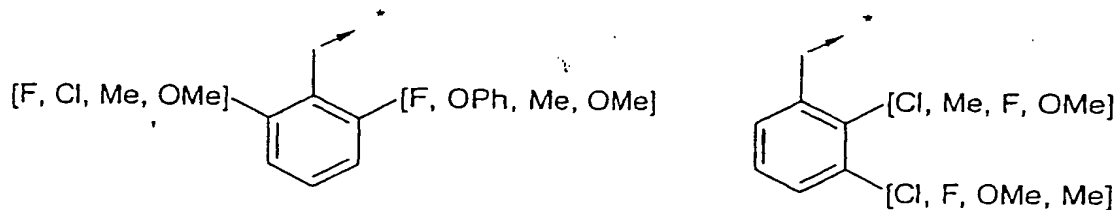


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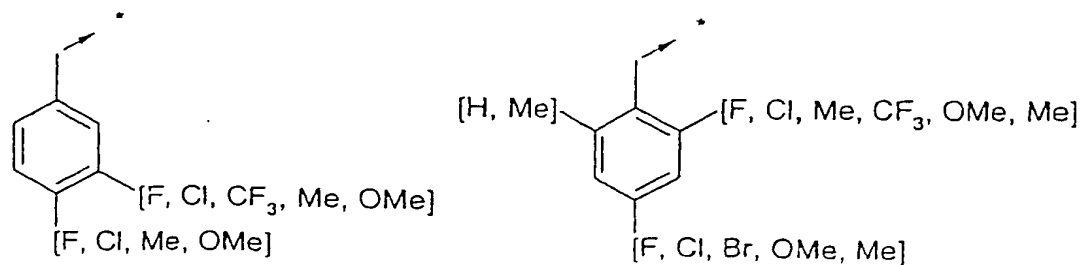
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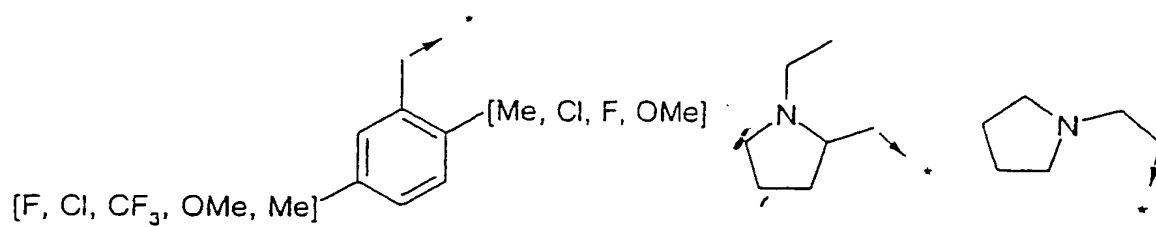
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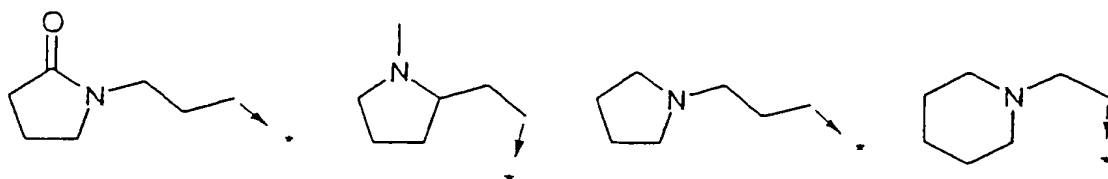




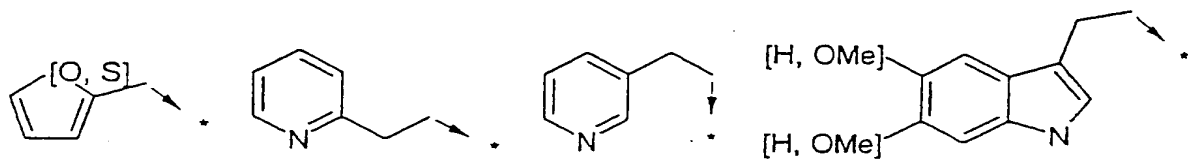
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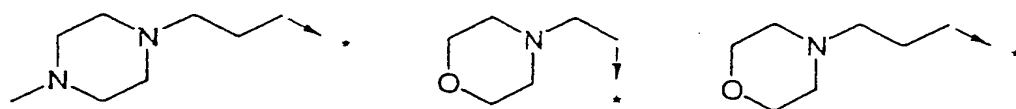
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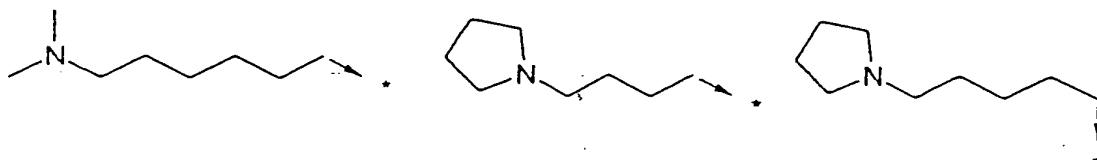
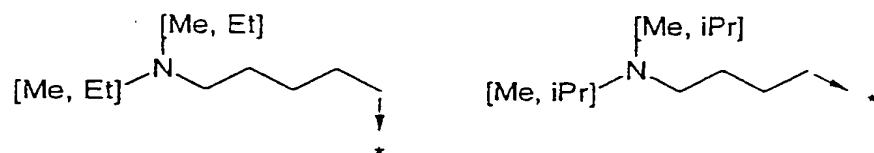
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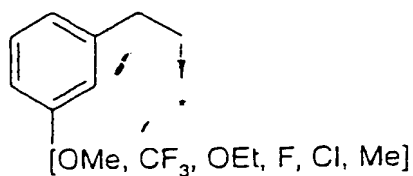
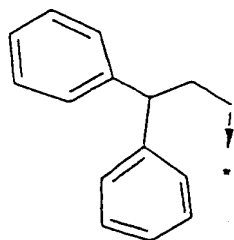
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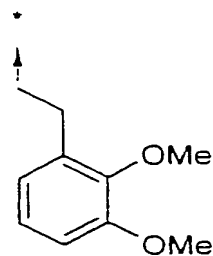
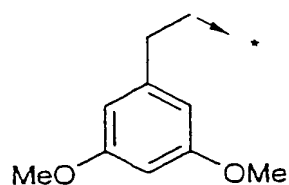
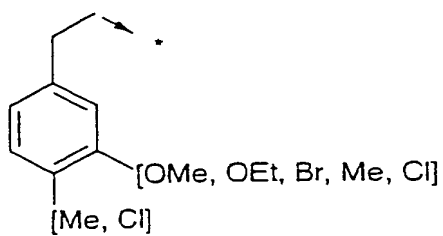
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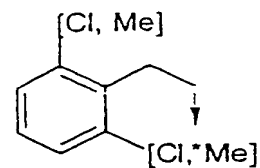
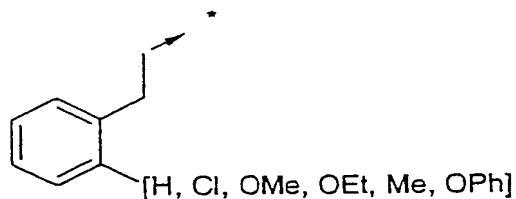
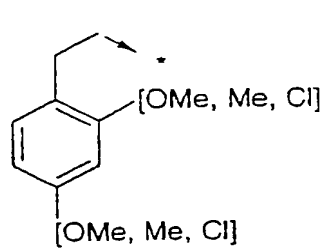
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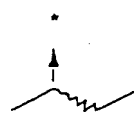
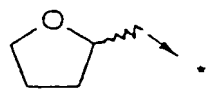
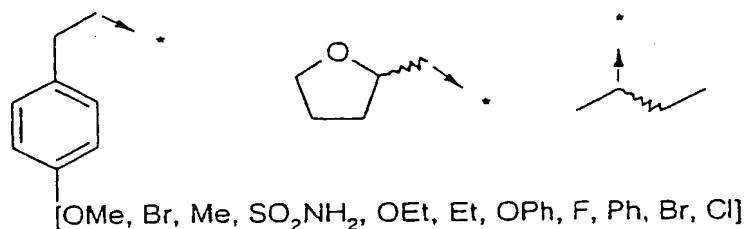
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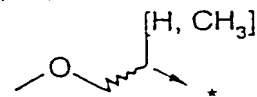
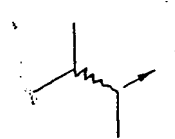
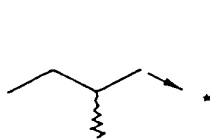
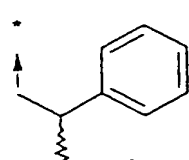
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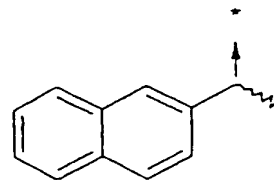
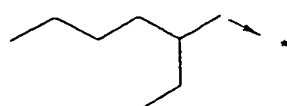
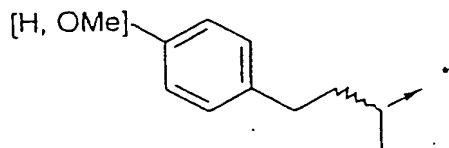
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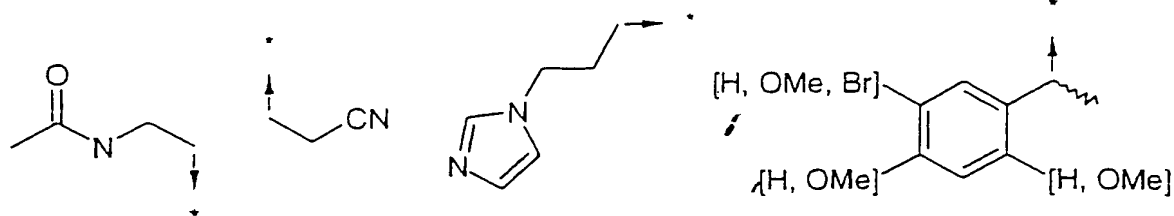
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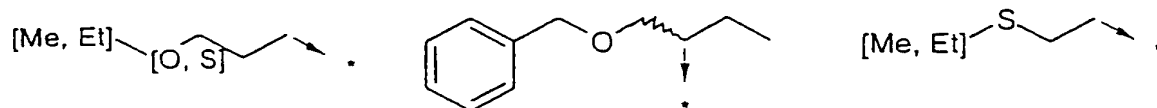
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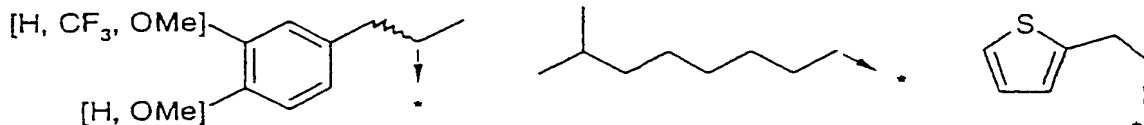
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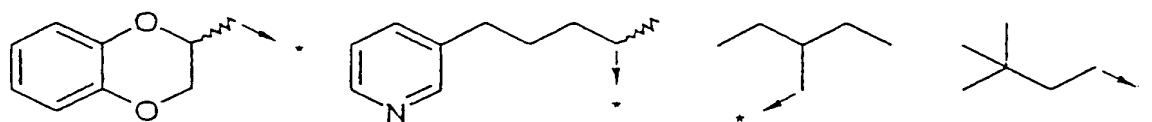
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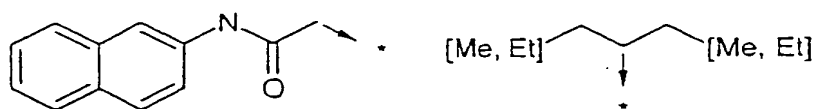
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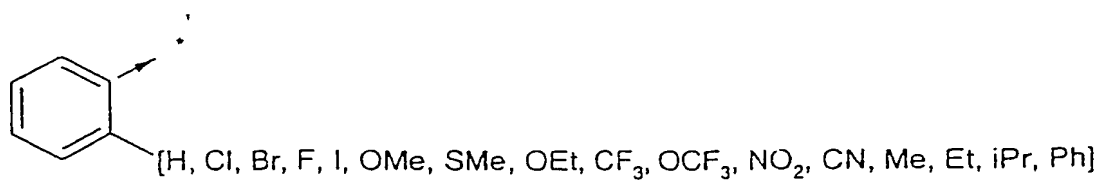


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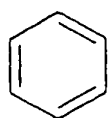


R2 represents one of the following radicals:

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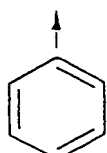


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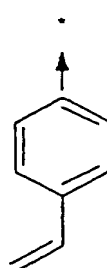
[Cl, Br, F, I, OMe, SMe, CF<sub>3</sub>, OCF<sub>3</sub>, NO<sub>2</sub>, CN, Me, Et, iPr, OCH<sub>2</sub>Ph]

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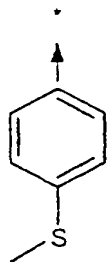


[Cl, Br, F, I, OMe, OEt, CF<sub>3</sub>, OCF<sub>3</sub>, NO<sub>2</sub>, CN, Me, Et, iPr, nBu, tBu, NMe<sub>2</sub>, NEt<sub>2</sub>]

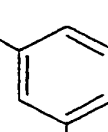
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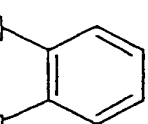
[Cl, CF<sub>3</sub>, Me, OMe]



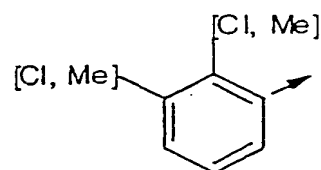
[Cl, CF<sub>3</sub>, Me, OMe]

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[Cl, OMe, Me, CF<sub>3</sub>, NO<sub>2</sub>]



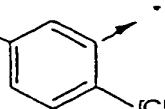
[Cl, Br, F, OMe, Me]



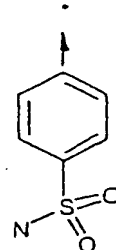
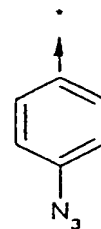
[Cl, Me]

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[Cl, Br, F, CF<sub>3</sub>, OMe, Me, NO<sub>2</sub>]

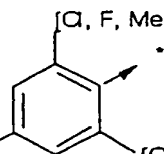


[Cl, Br, F, OMe, Me]



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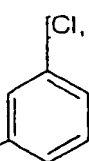
[Cl, F, Me]



[Cl, F, Me]

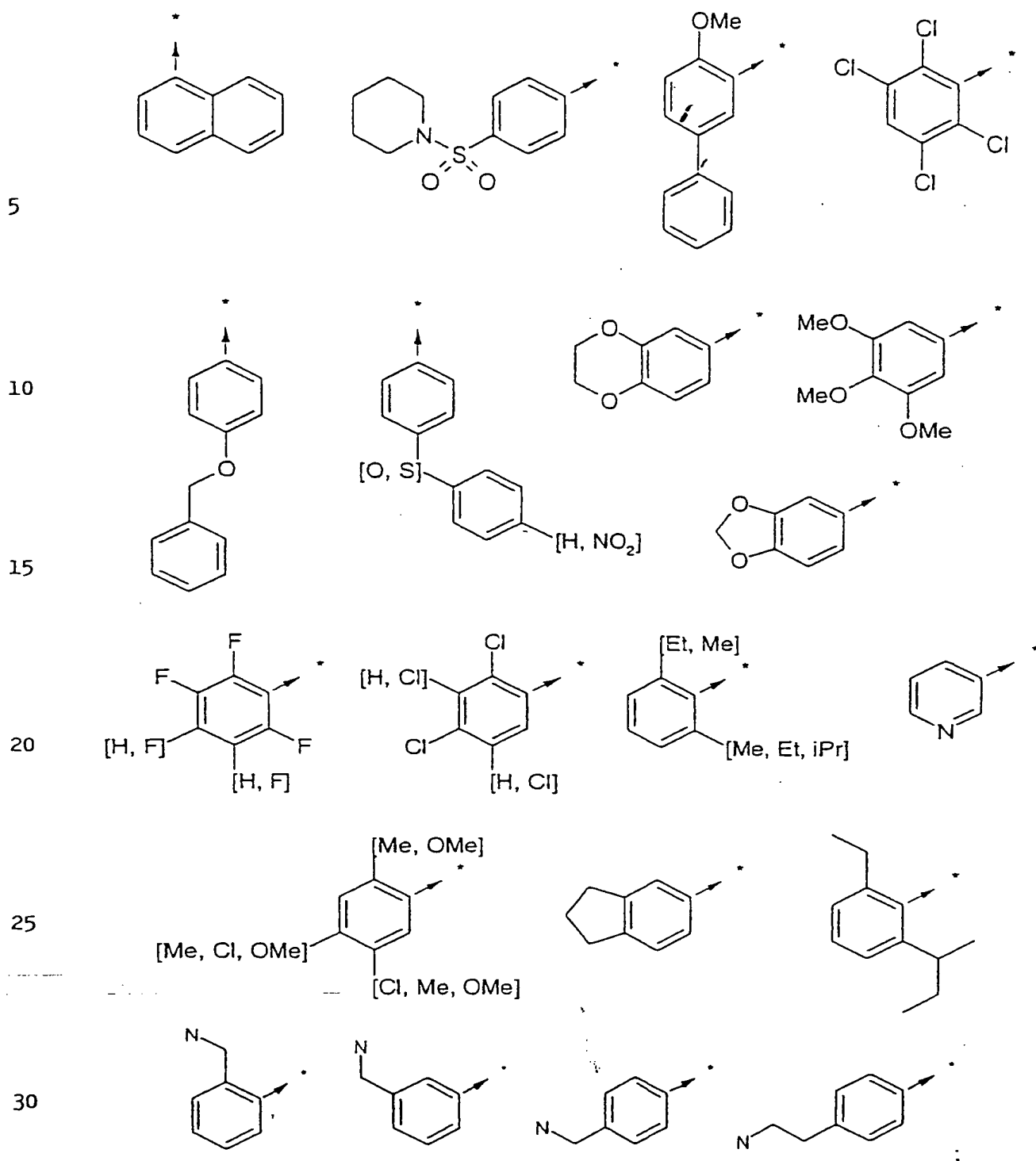
[H, Cl, Br, F, Me]

[Cl, Br, F, Me, OMe, CF<sub>3</sub>, OCF<sub>3</sub>, NO<sub>2</sub>]

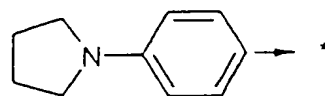
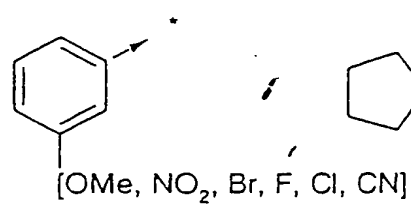
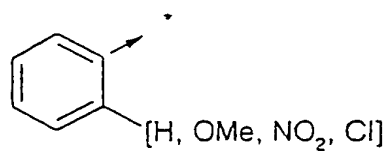


[Cl, Br, F, Me, OMe, NO<sub>2</sub>, iPr, CF<sub>3</sub>]

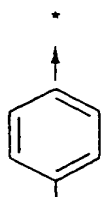
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R3 represents CO-R5 or one of the following radicals:

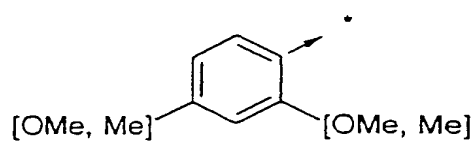
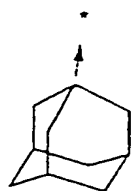
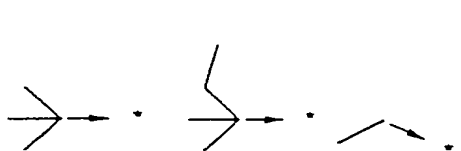


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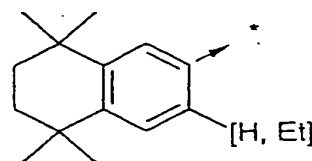
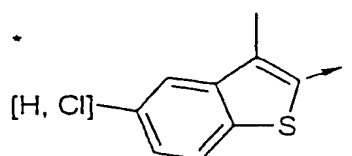
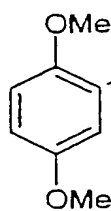


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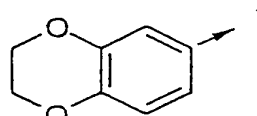
[Br, Cl, F, OMe, Ph, Me, NO<sub>2</sub>, N<sub>3</sub>, OCF<sub>3</sub>, CN, CF<sub>3</sub>, NEt<sub>2</sub>, nC<sub>4</sub>H<sub>9</sub>, nC<sub>5</sub>H<sub>11</sub>, OCH<sub>2</sub>Ph]



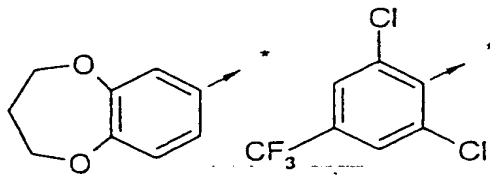
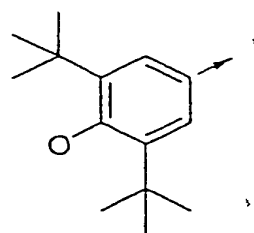
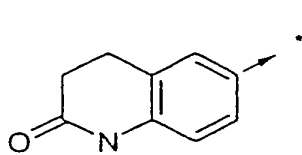
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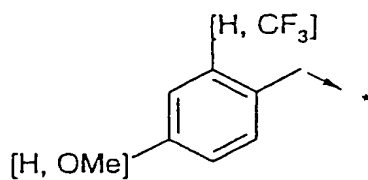
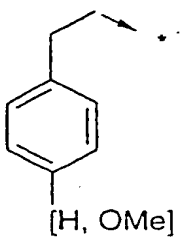
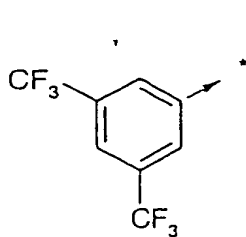
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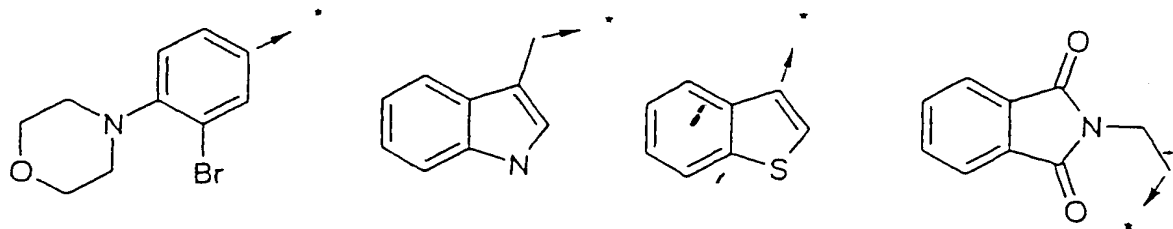
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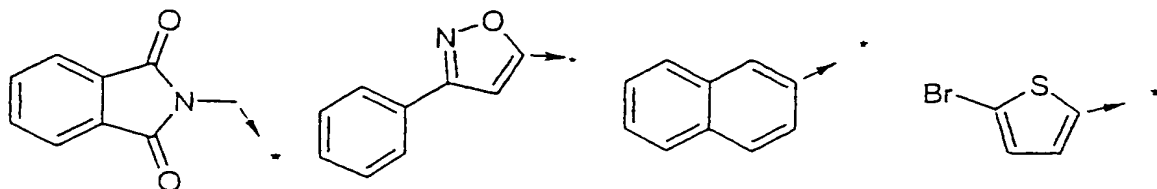
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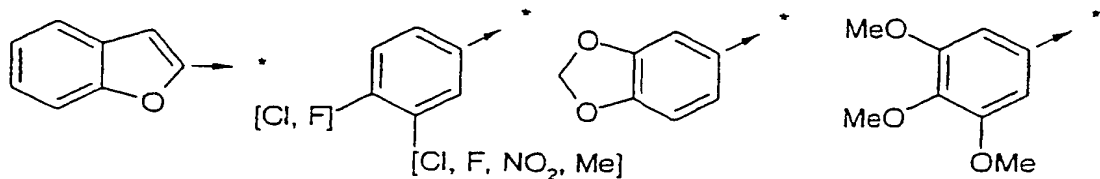
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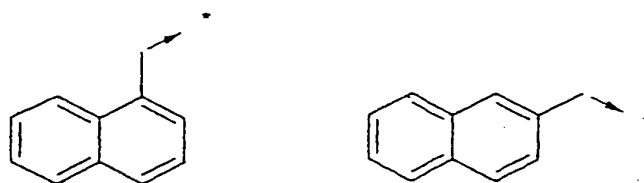
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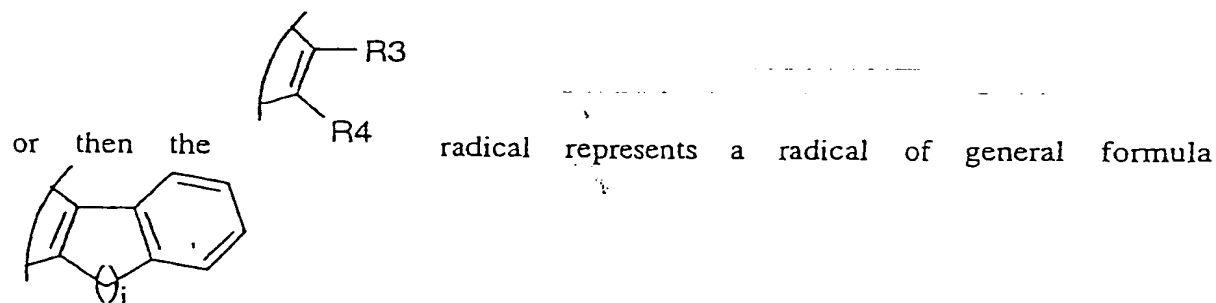
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R4 represents H, alkyl, carbocyclic or heterocyclic aralkyl optionally substituted on the aryl radical;

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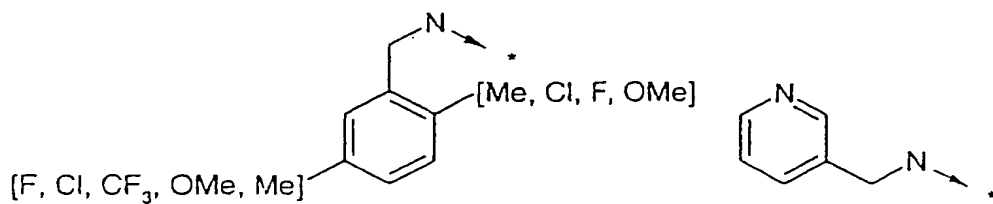
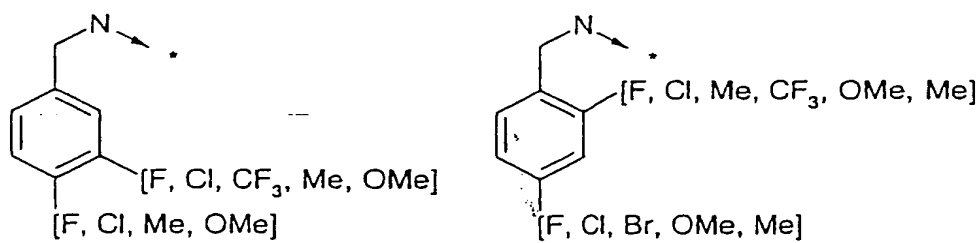
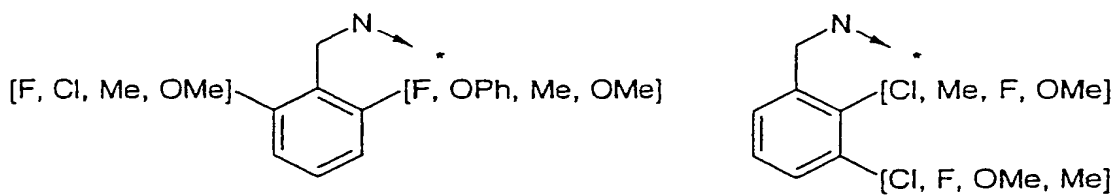
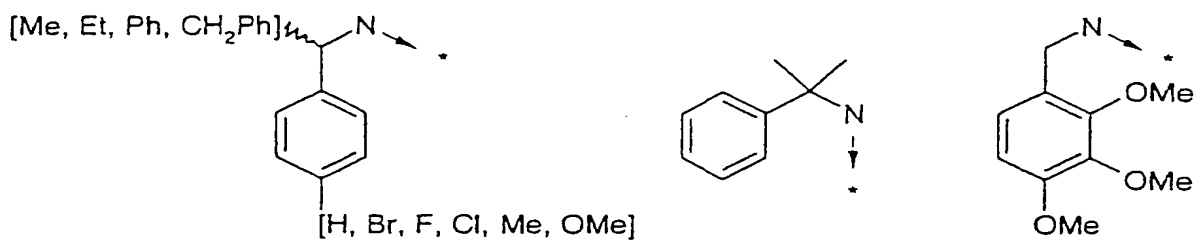
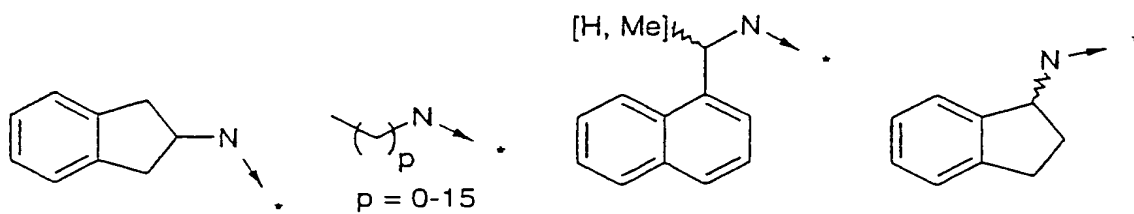
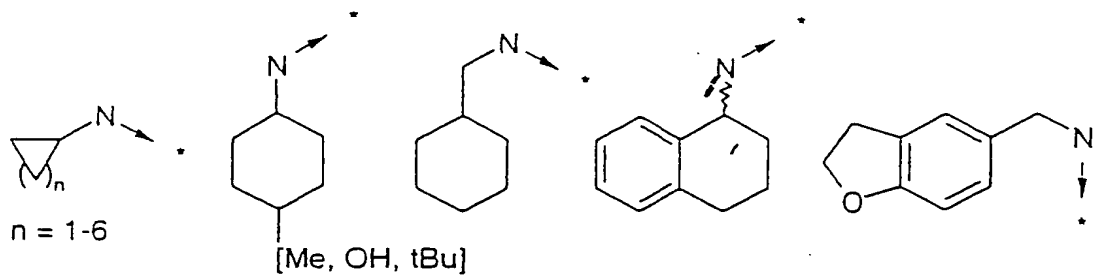


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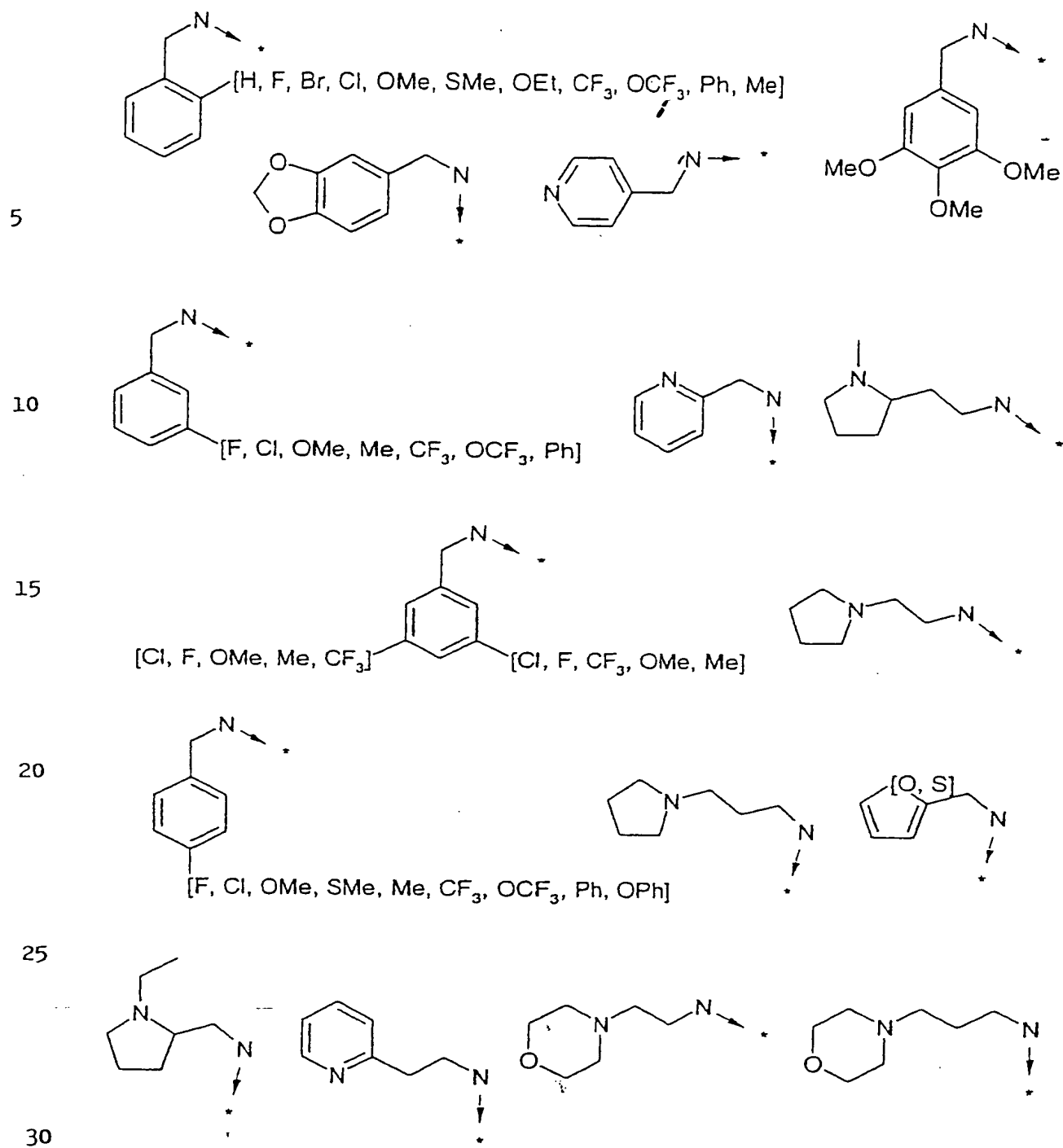
in which i represents an integer from 1 to 3;

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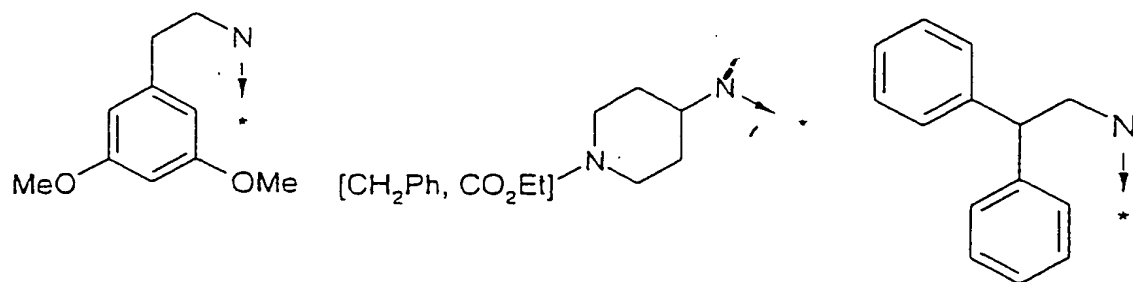
R5 represents one of the following radicals:



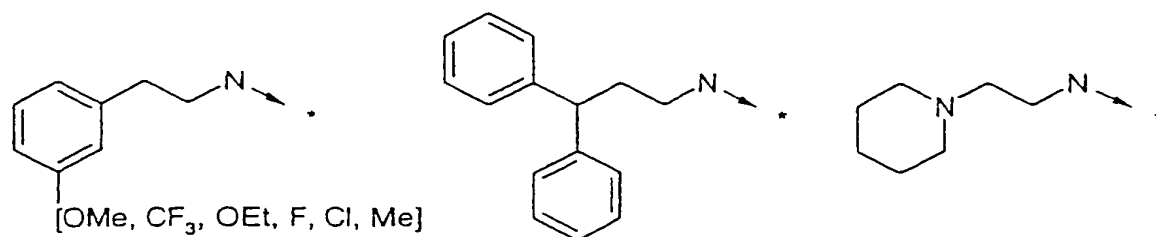




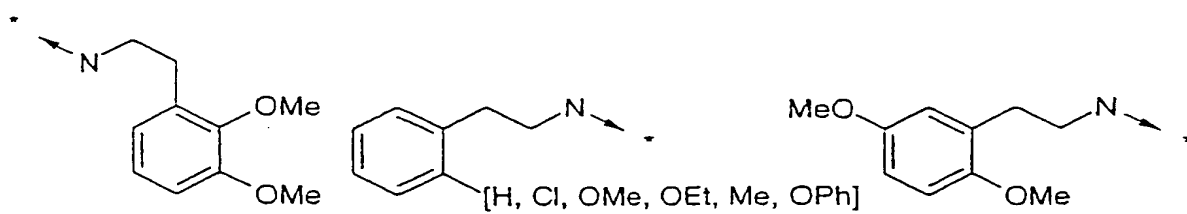
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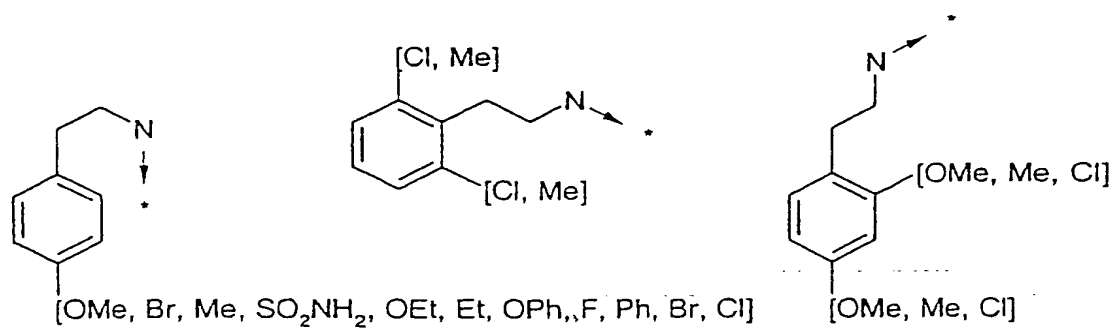
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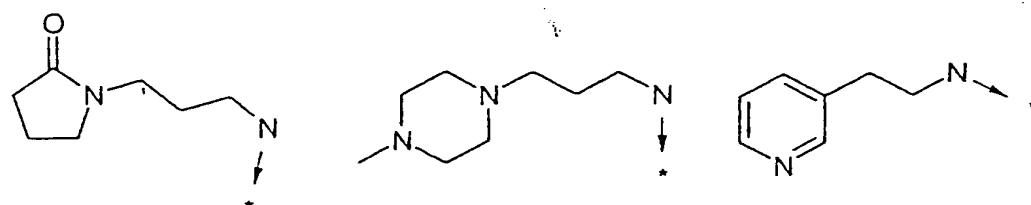
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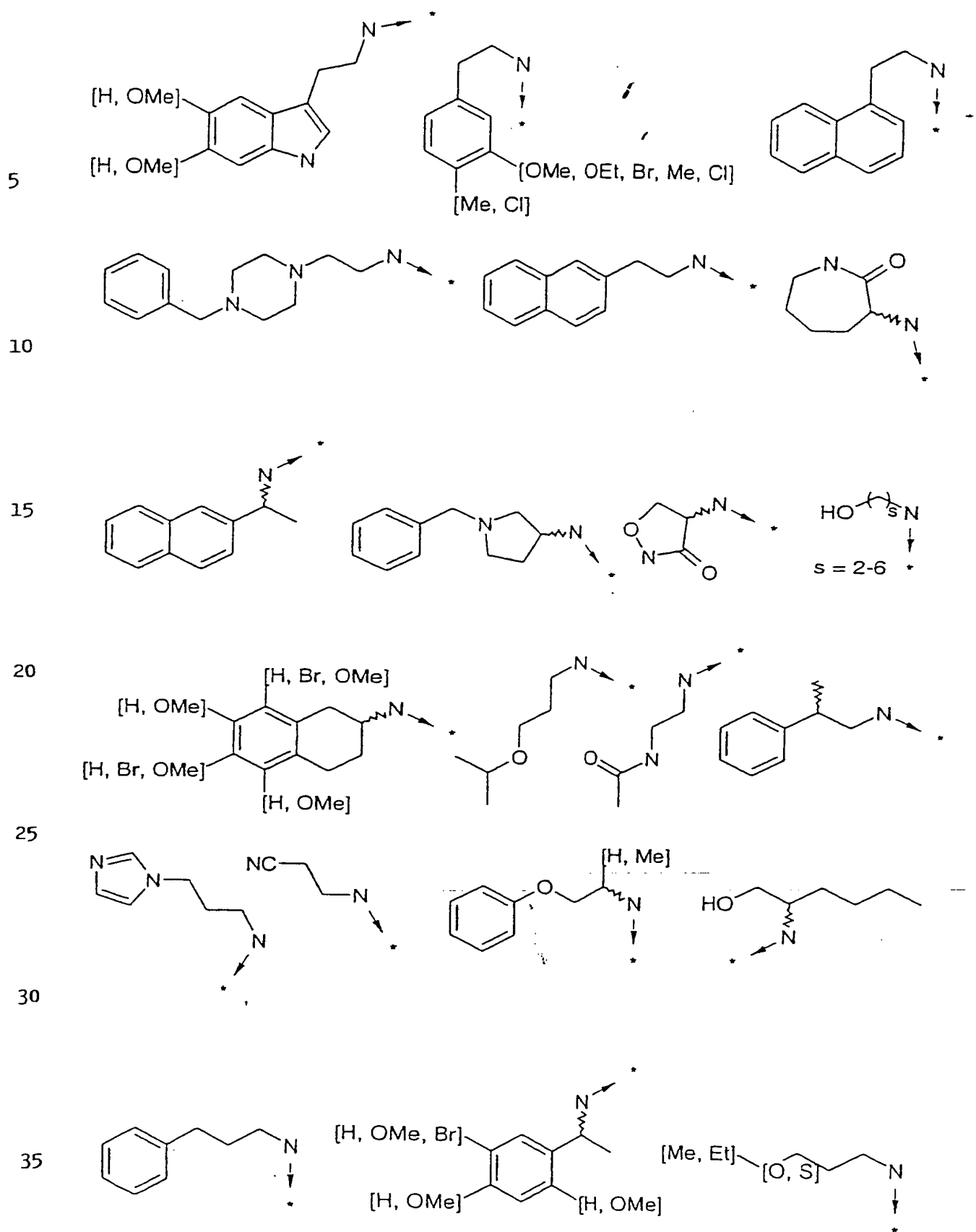


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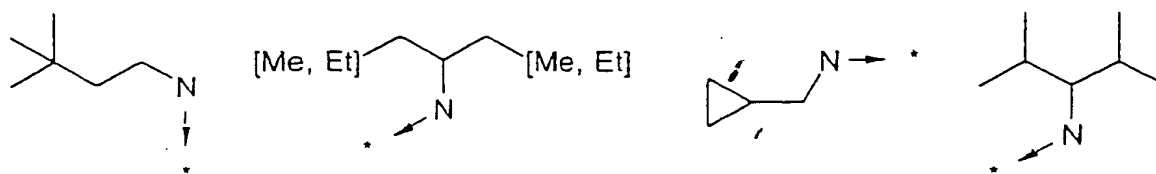


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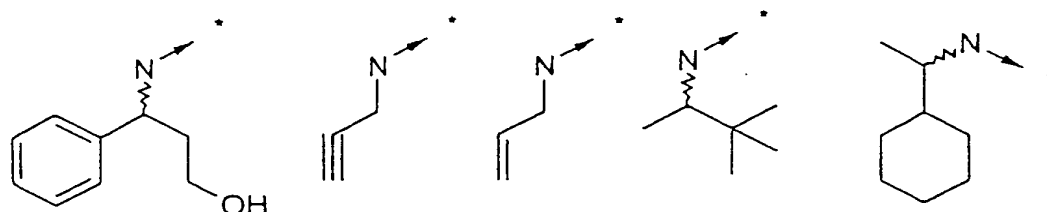
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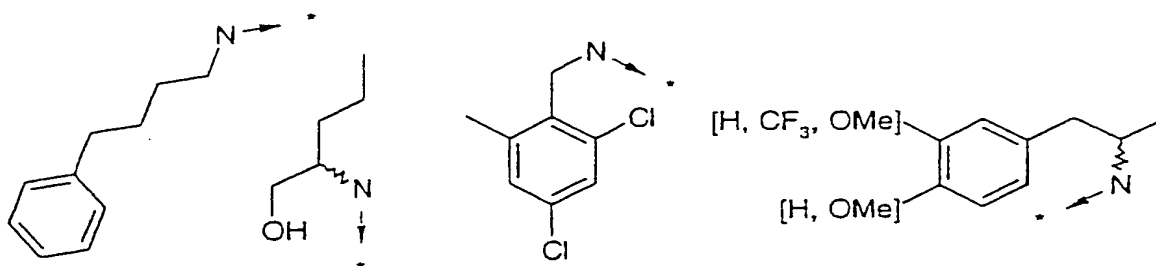
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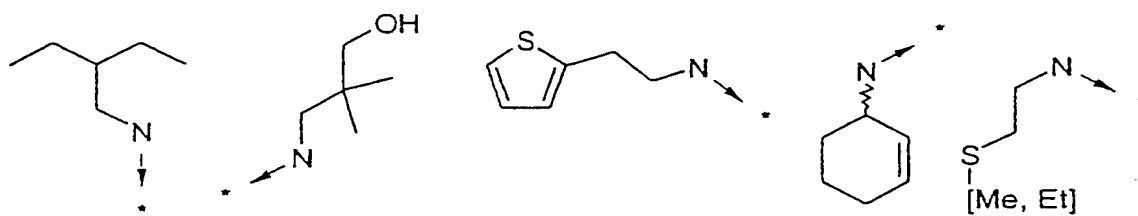
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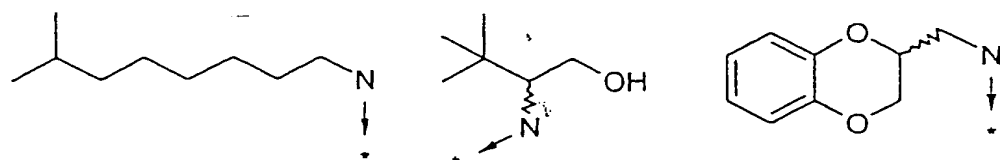


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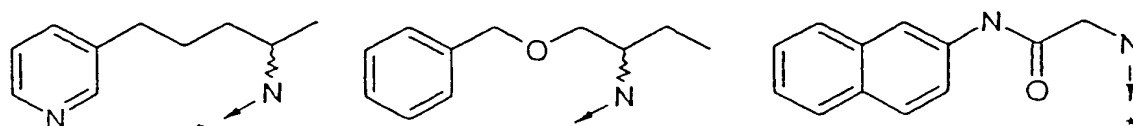


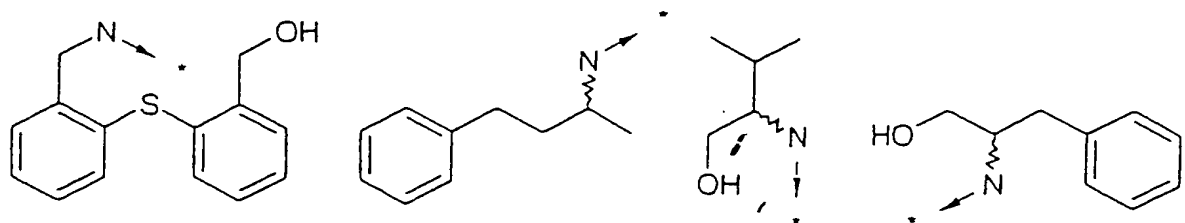
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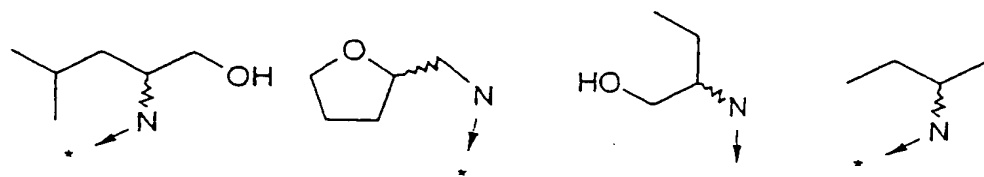


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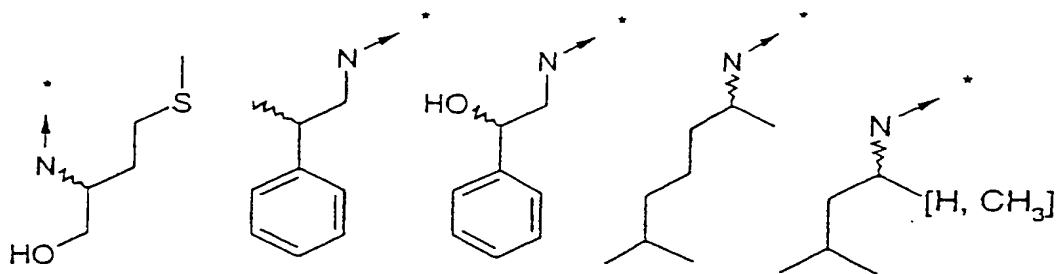




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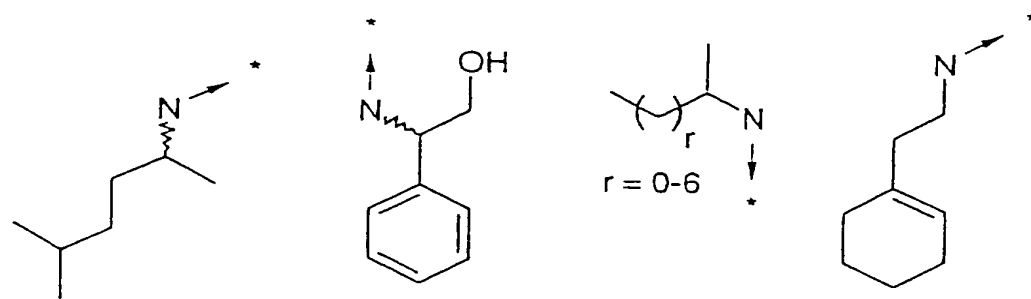


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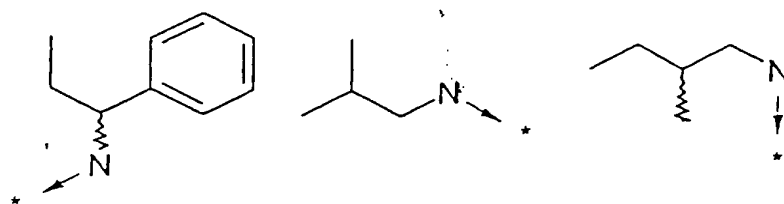


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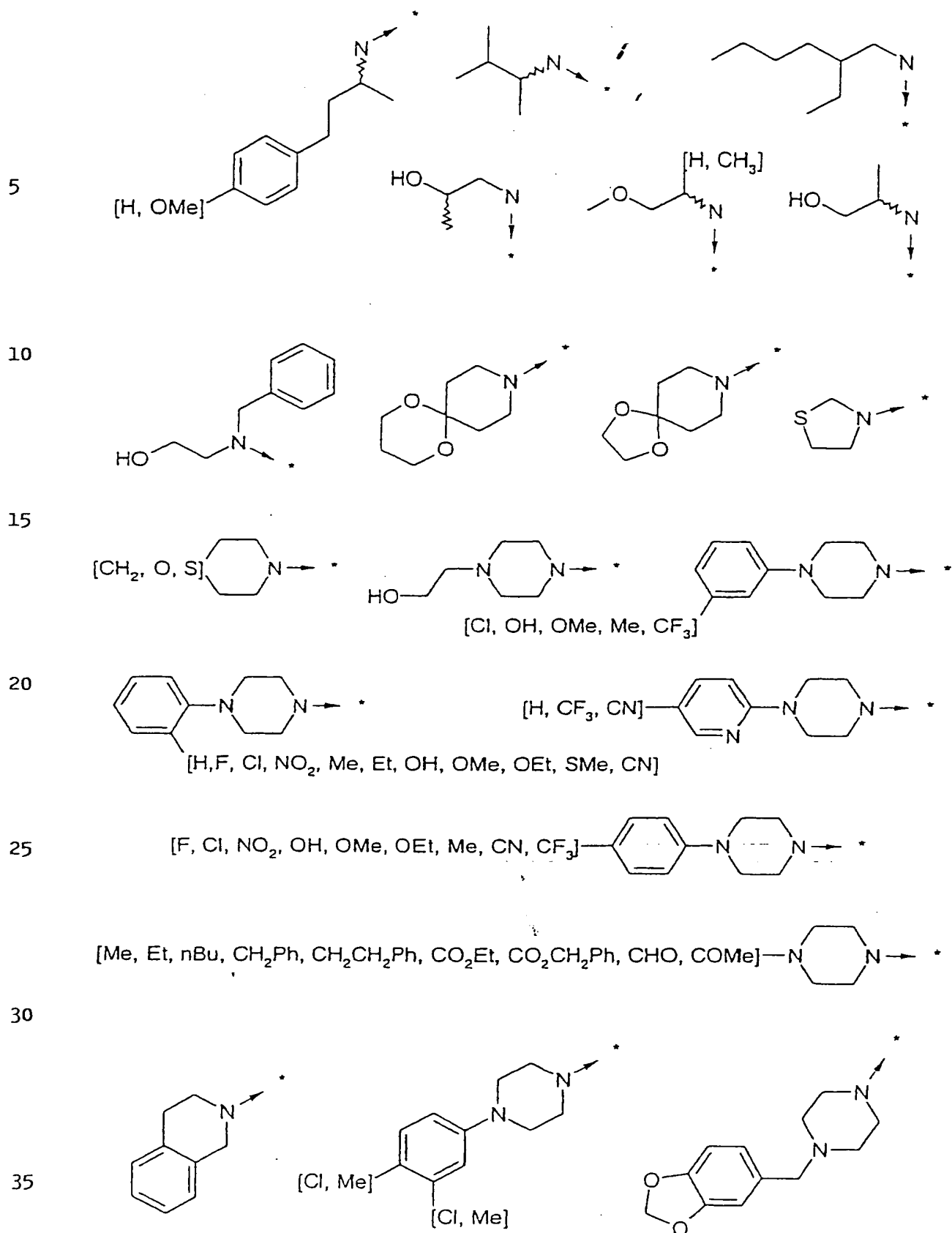
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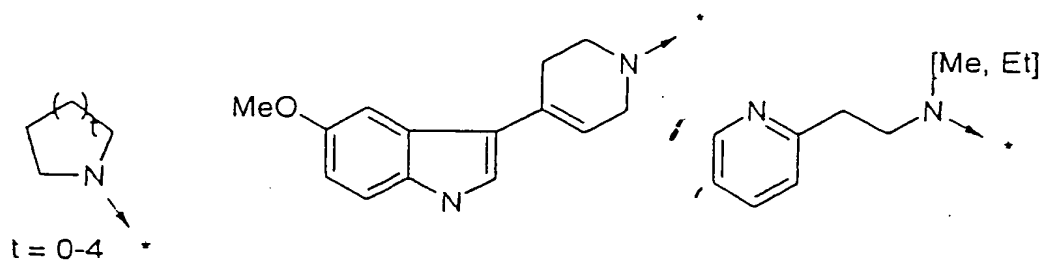
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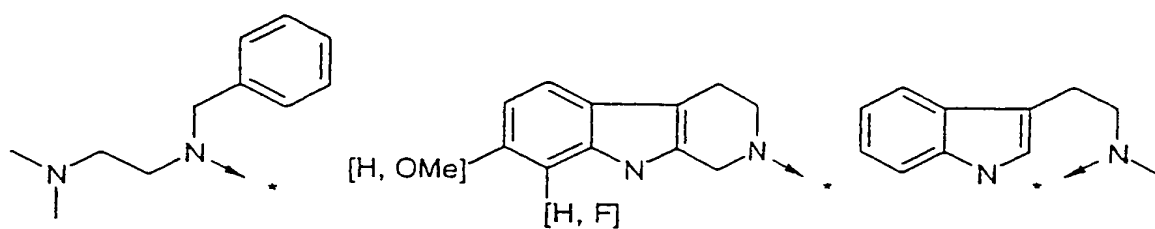
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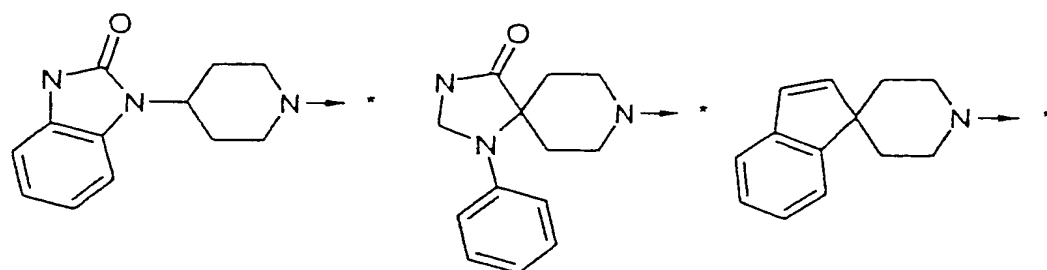
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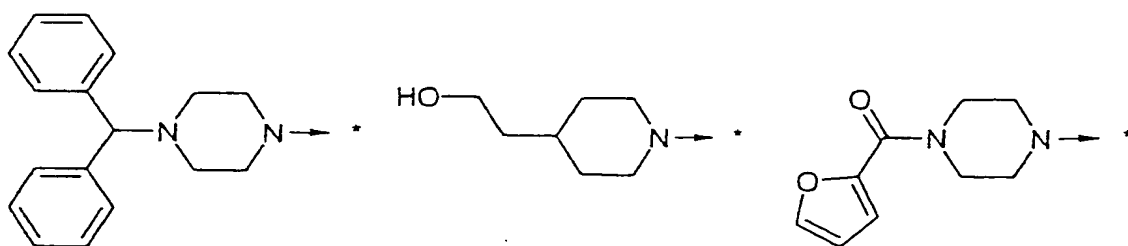
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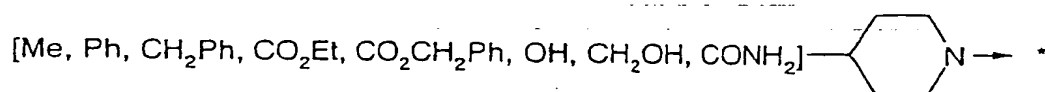
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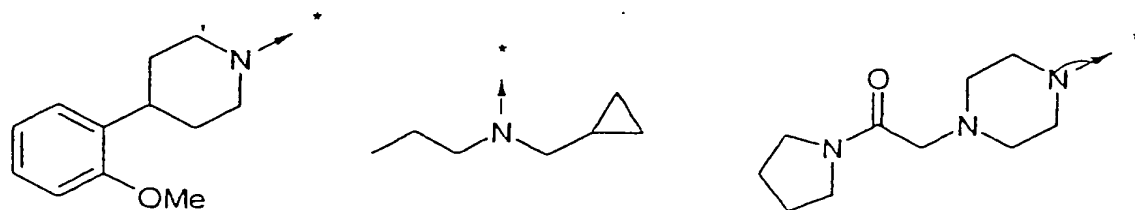
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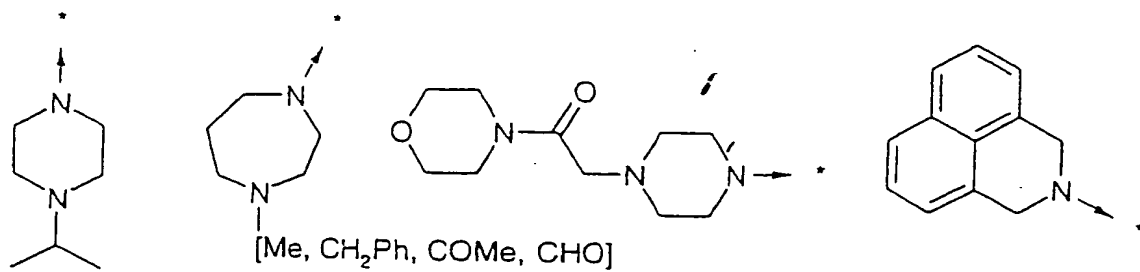


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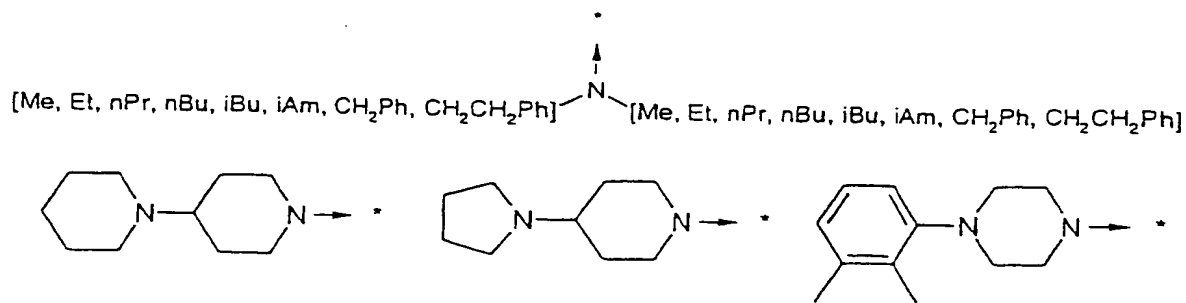


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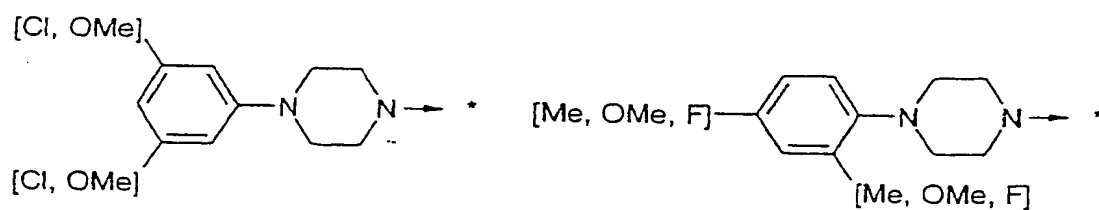
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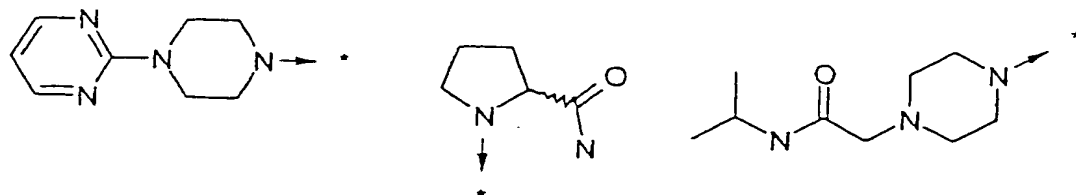
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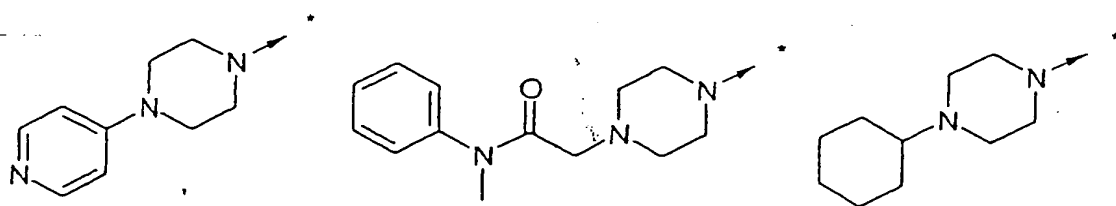
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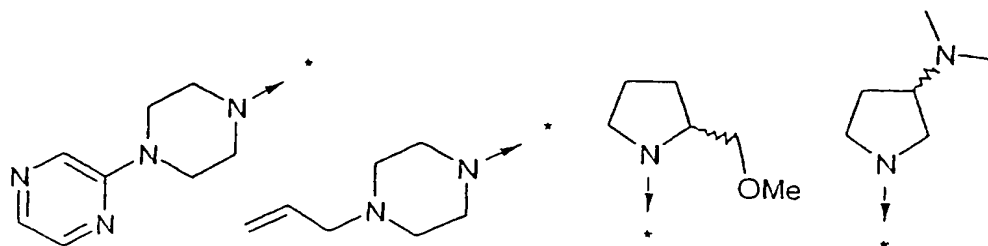


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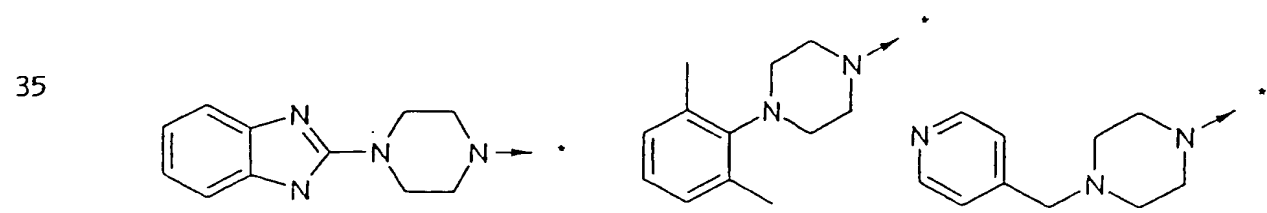
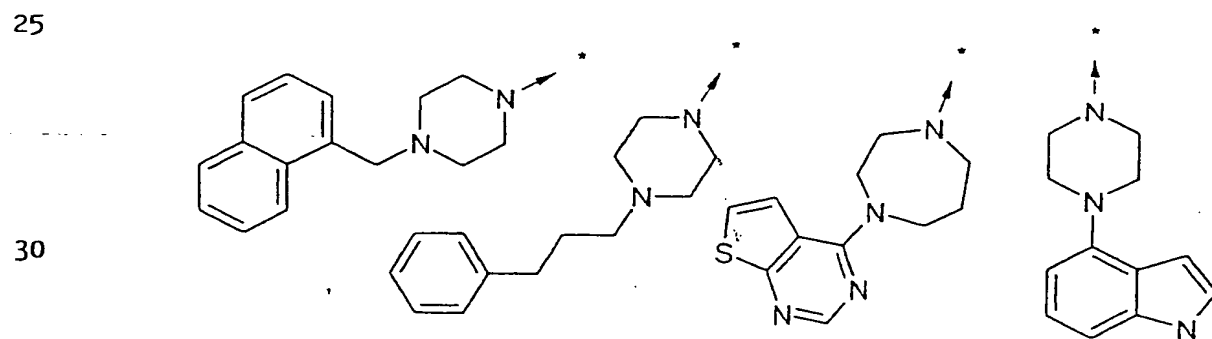
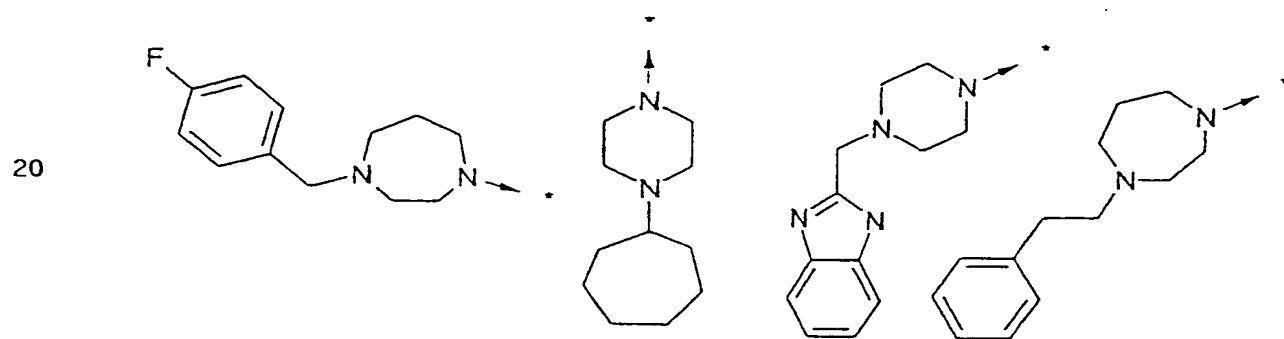
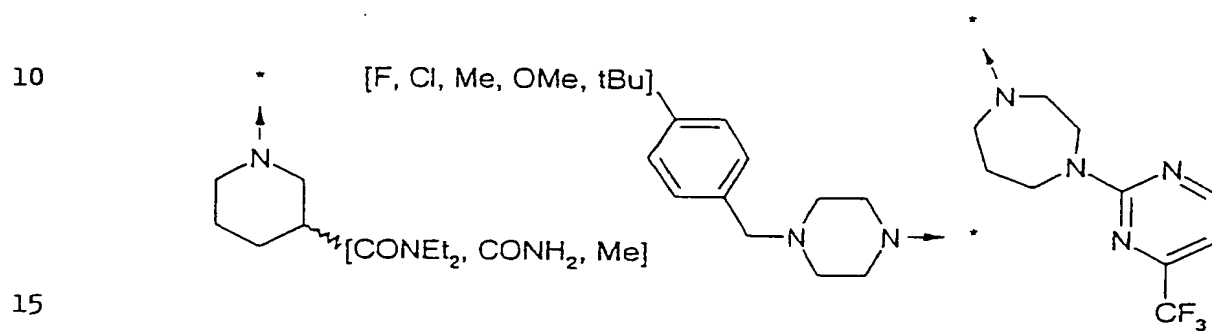
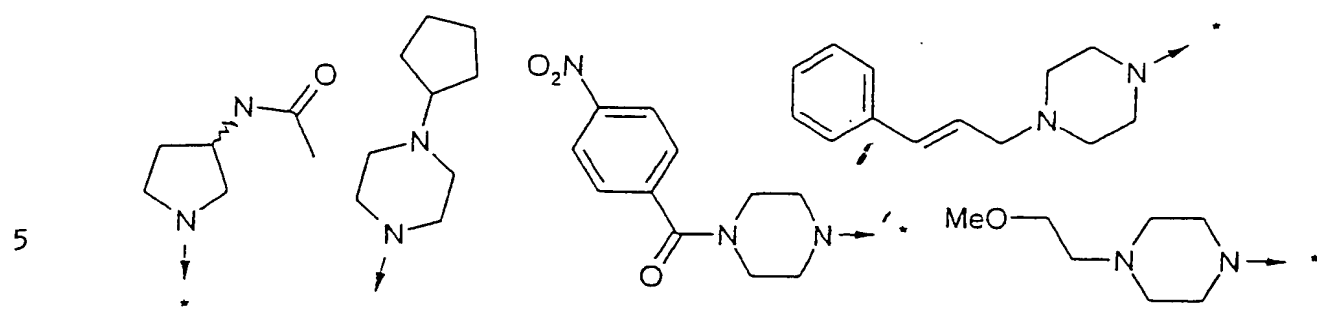


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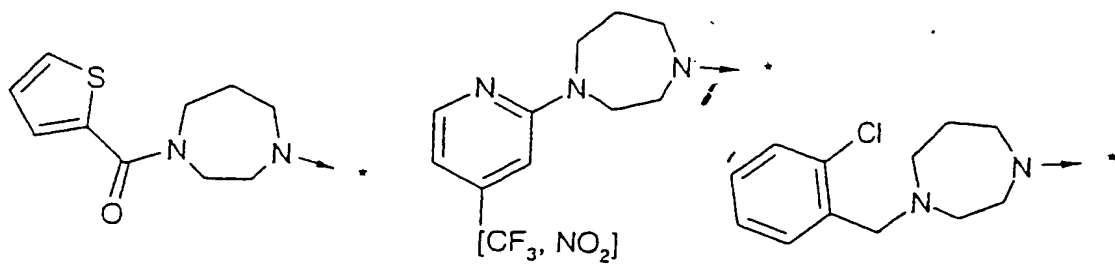
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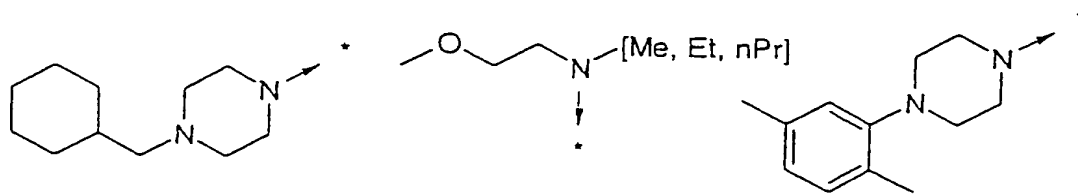




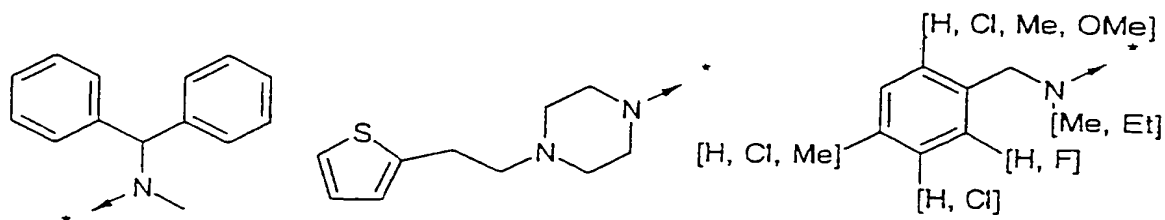
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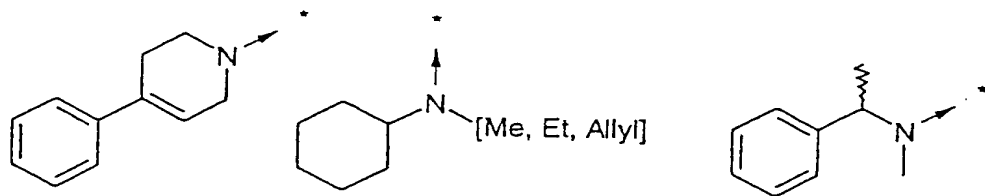
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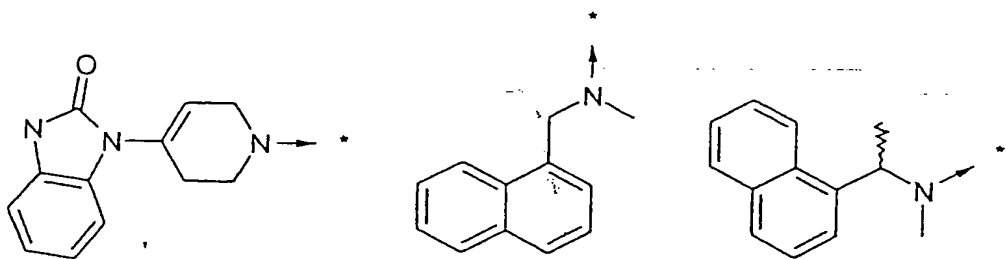
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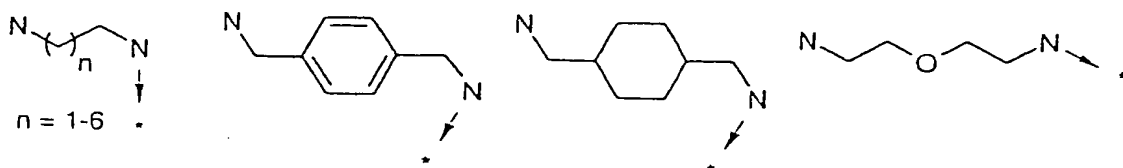
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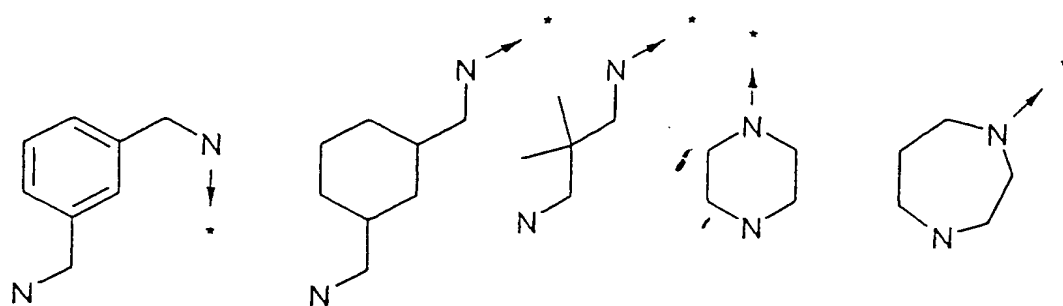


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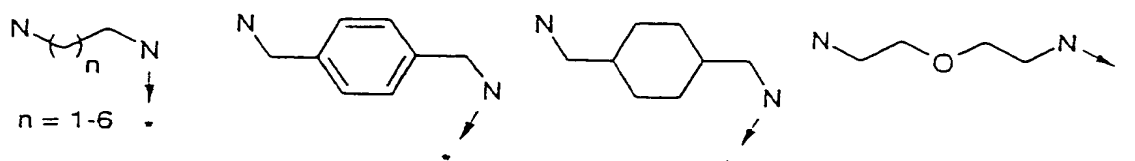
5



R10

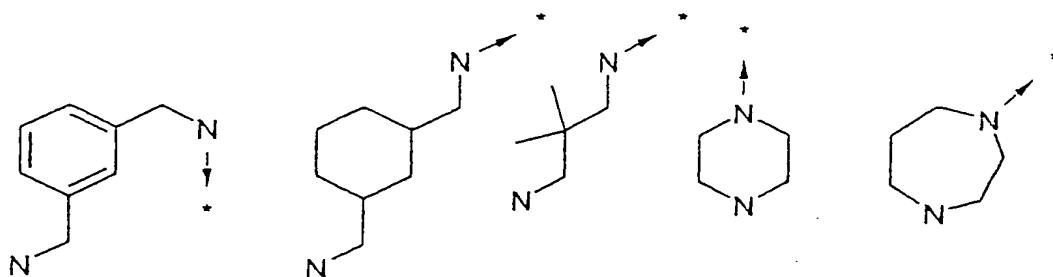
represents one of the following radicals:

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R11

represents H;

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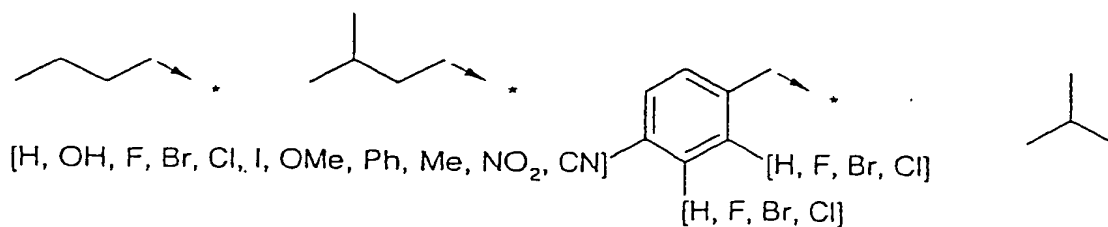
R12

represents one of the following radicals:

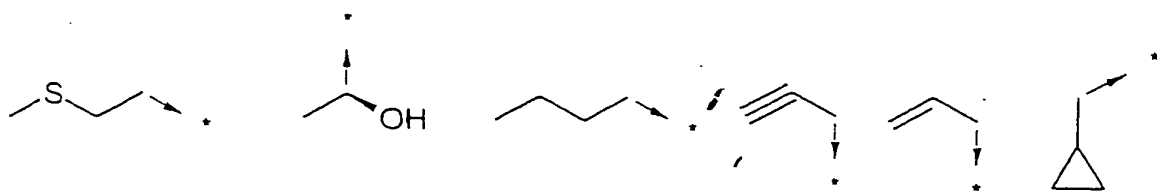
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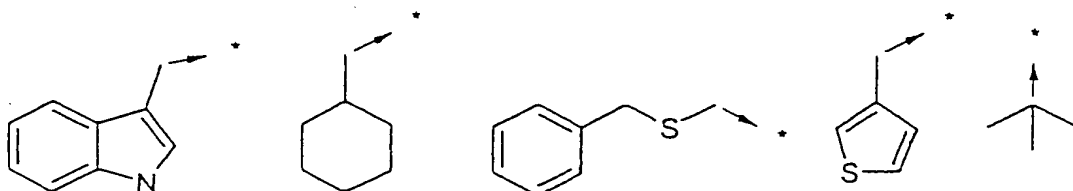
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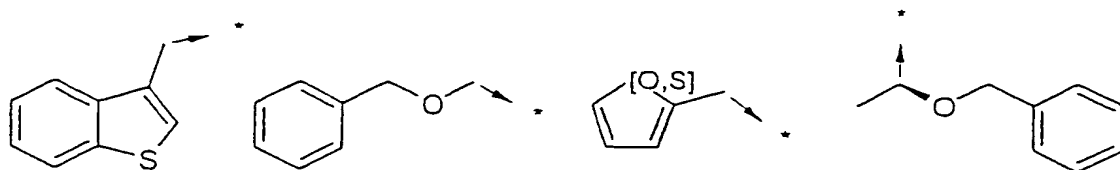
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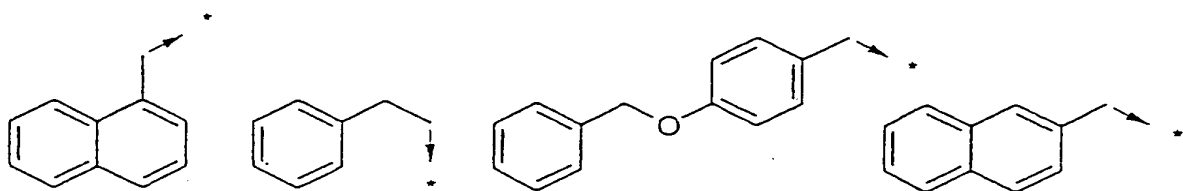
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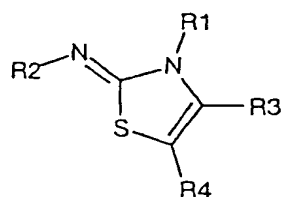
it being understood that for R<sub>4</sub>, when the aryl group is substituted, it can be from 1 to 5 times (other than the bond which links it with the remainder of the molecule) by radicals chosen independently from the group comprising a halogen atom and an alkyl or alkoxy radical.

The compounds of the invention are preferably such that R<sub>4</sub> represents H.

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More preferentially, the compounds according to the invention correspond to general formula (II)

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(II)

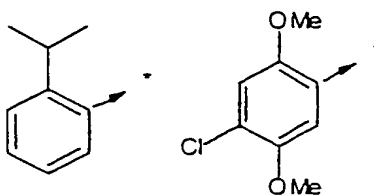
in which:

- either R1 represents one of the radicals below



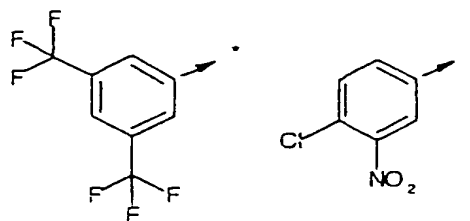
5

R2 represents one of the radicals below



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R3 represents one of the radicals below



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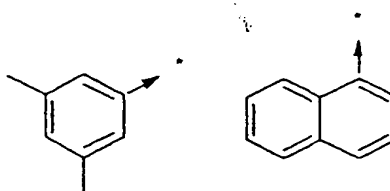
and R4 represents H;

- or also R1 represents one of the radicals below



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R2 represents one of the radicals below



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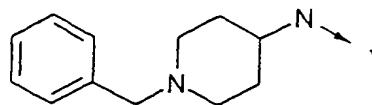
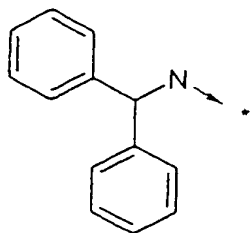
R3 represents COR5,

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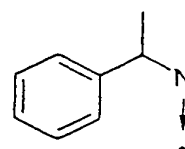
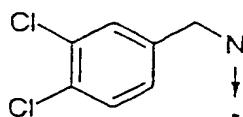
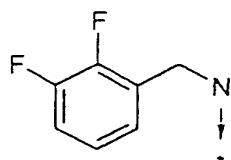
R4 represents H,

and R5 represents one of the radicals below

5



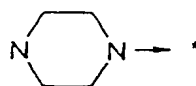
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- or finally R1 represents the  $-C(R11)(R12)-CO-R10$  radical in which

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R10 represents the radical

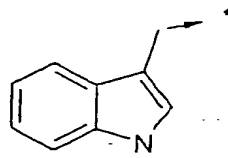


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R11 represents H

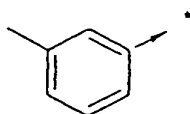
and R12 represents the radical

25



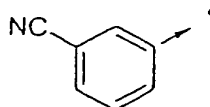
R2 represents the radical

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R3 represents the radical

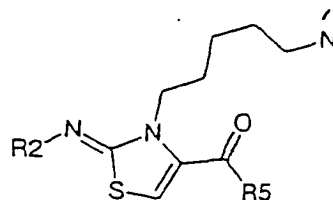
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and R4 represents H.

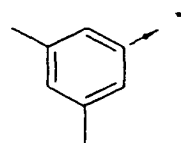
The invention also relates to a compound characterized in that it corresponds:

- to formula



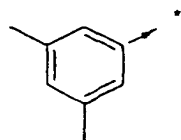
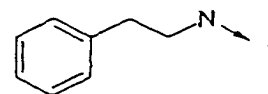
(i)

in which:



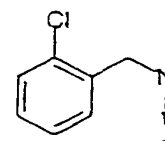
- R2 represents the radical,

radical and R5 represents the

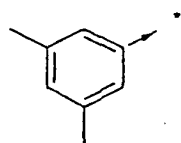


- R2 represents the

radical and R5 represents the

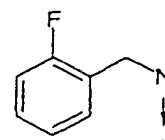


radical,

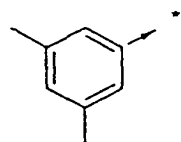


- R2 represents the

radical and R5 represents the

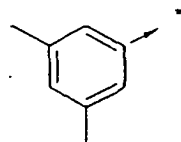
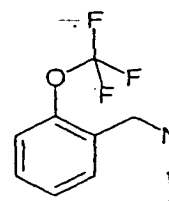


radical,



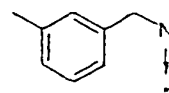
- R2 represents the radical,

radical and R5 represents the

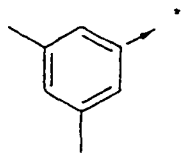


- R2 represents the

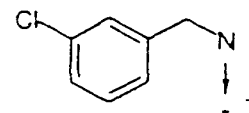
radical and R5 represents the



radical,

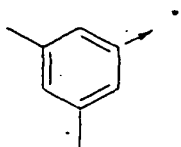


- R2 represents the radical,

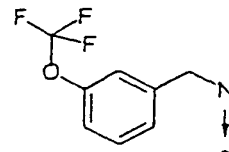


radical and R5 represents the

5

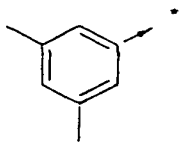


- R2 represents the radical,

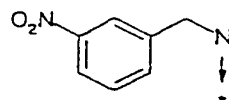


radical and R5 represents the

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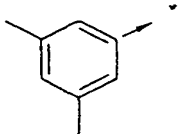


- R2 represents the radical,

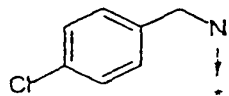


radical and R5 represents the

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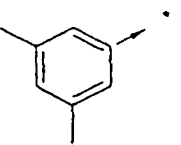


- R2 represents the radical,

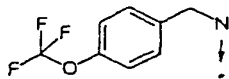


radical and R5 represents the

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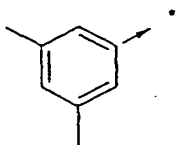


- R2 represents the radical,

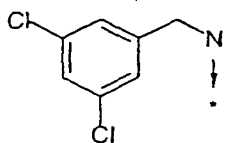


radical and R5 represents the

25



- R2 represents the radical,



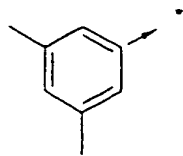
radical and R5 represents the

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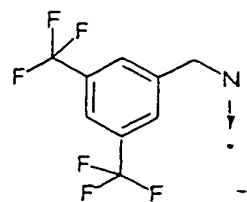
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- R2 represents the radical,

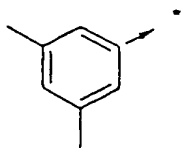


radical and R5 represents the

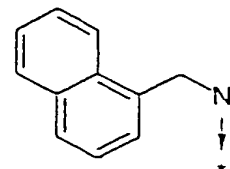


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- R2 represents the radical,

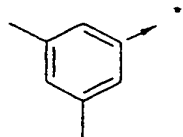


radical and R5 represents the

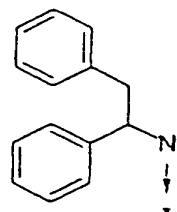


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- R2 represents the



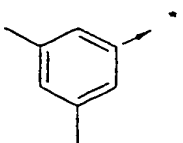
radical and R5 represents the



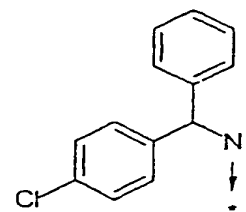
radical,

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- R2 represents the radical,



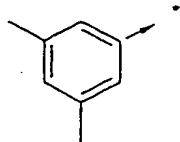
radical and R5 represents the



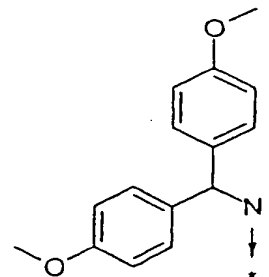
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- R2 represents the radical,



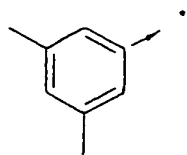
radical and R5 represents the



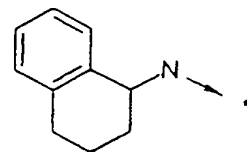
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- R2 represents the radical,

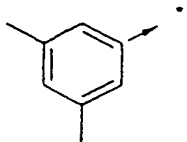


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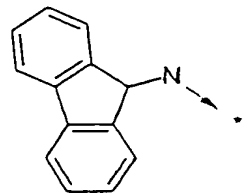


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- R2 represents the radical,

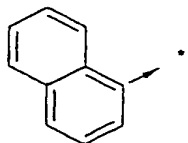


radical and R5 represents the

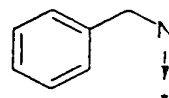


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- R2 represents the



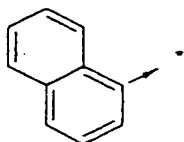
radical and R5 represents the



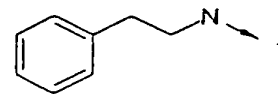
radical,

15

- R2 represents the radical,

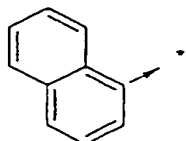


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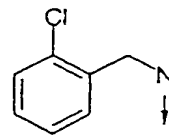


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- R2 represents the



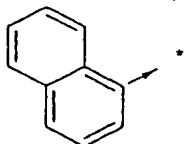
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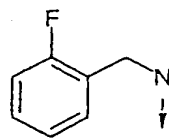
radical,

25

- R2 represents the



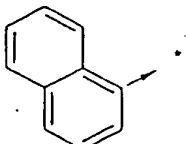
radical and R5 represents the



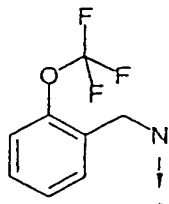
radical,

30

- R2 represents the

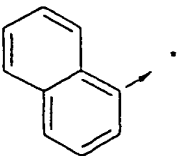
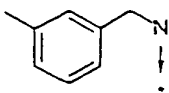


radical and R5 represents the

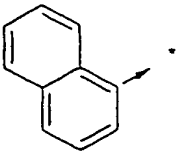
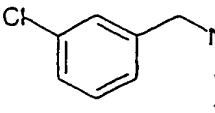


radical,

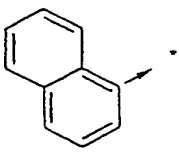
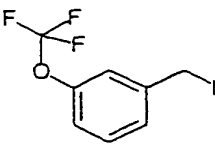
35

- R2 represents the  radical and R5 represents the  radical,

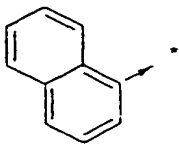
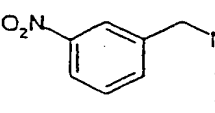
5

- R2 represents the  radical and R5 represents the  radical,

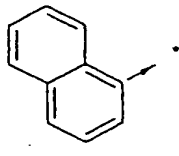
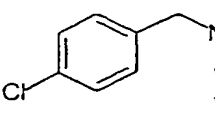
10

- R2 represents the  radical and R5 represents the  radical,

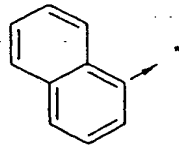
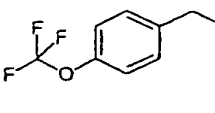
15

- R2 represents the  radical and R5 represents the  radical,

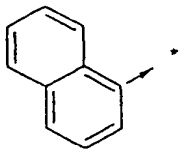
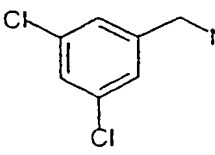
20

- R2 represents the  radical and R5 represents the  radical,

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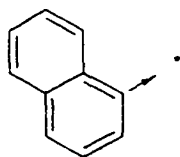
- R2 represents the  radical and R5 represents the  radical,

30

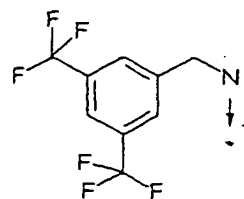
- R2 represents the  radical and R5 represents the  radical,

35

- R2 represents the radical,

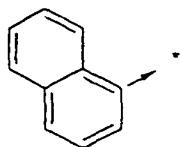


radical and R5 represents the

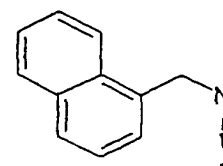


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- R2 represents the radical,

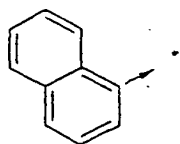


radical and R5 represents the

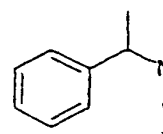


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- R2 represents the



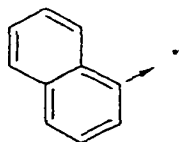
radical and R5 represents the



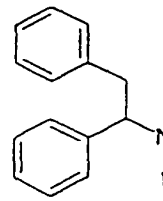
radical,

15

- R2 represents the



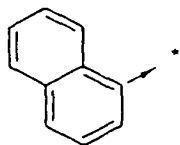
radical and R5 represents the



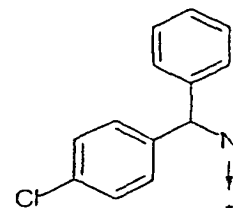
radical,

20

- R2 represents the radical,



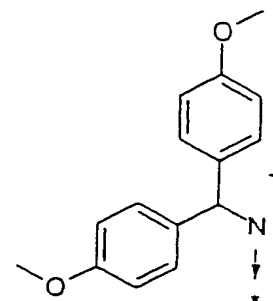
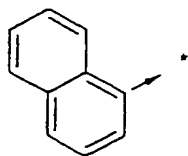
radical and R5 represents the



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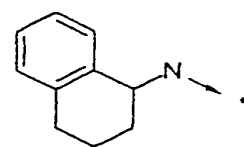
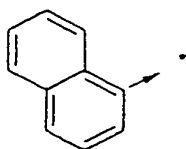
5



- R2 represents the radical,

radical and R5 represents the

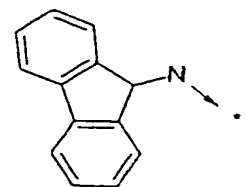
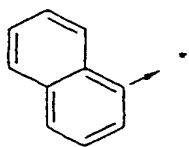
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- R2 represents the radical, or finally

radical and R5 represents the

15



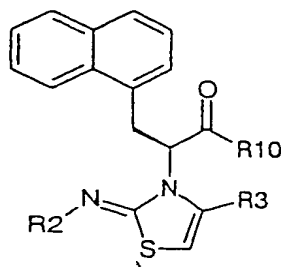
- R2 represents the radical;

radical and R5 represents the

20

• to formula

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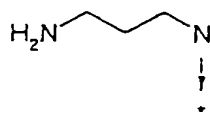
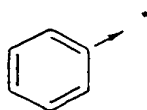
(ii)

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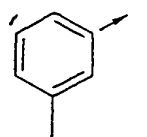
in which:

5

- R10 represents



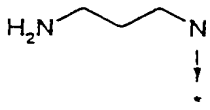
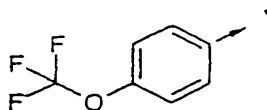
, R2 represents



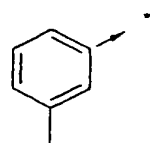
and R3 represents

10

- R10 represents



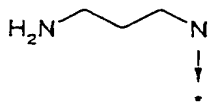
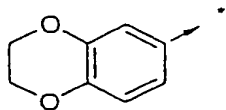
, R2 represents



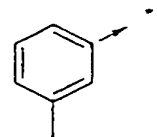
and R3 represents

15

- R10 represents



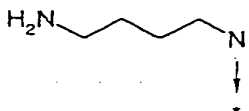
, R2 represents



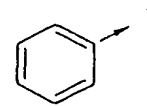
and R3 represents

20

- R10 represents



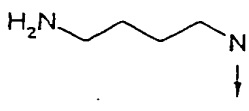
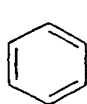
, R2 represents



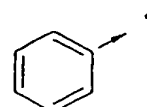
and R3 represents

25

- R10 represents



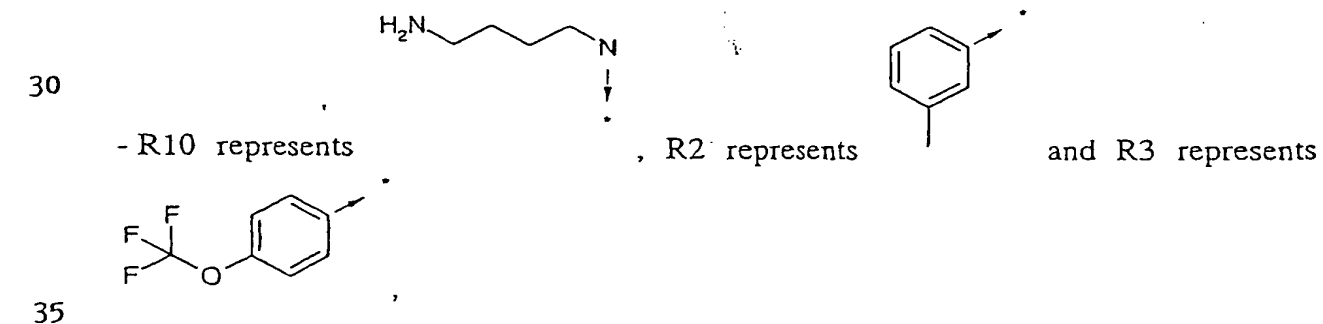
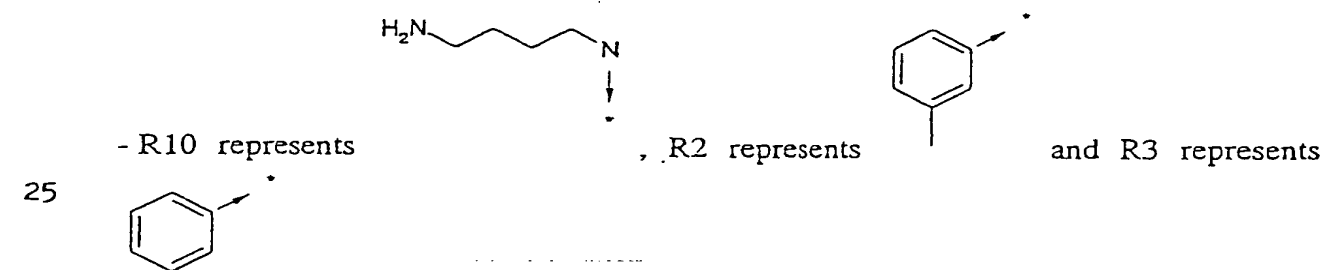
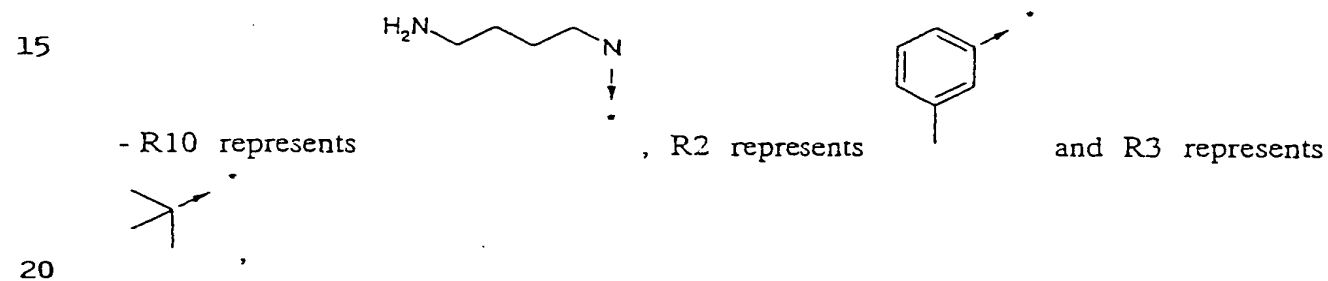
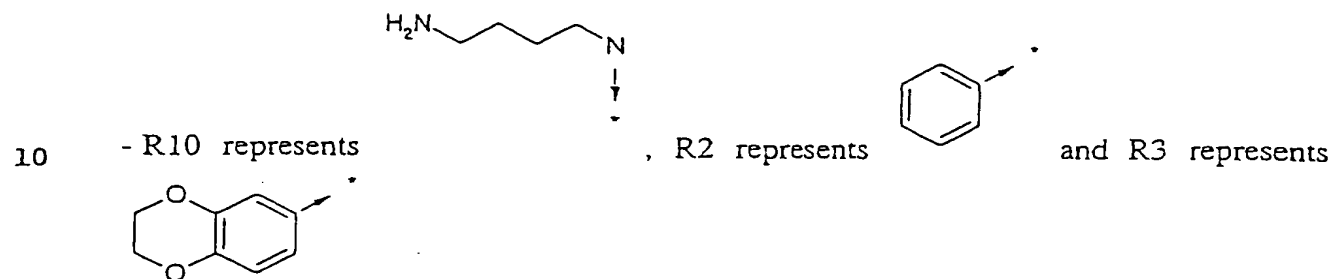
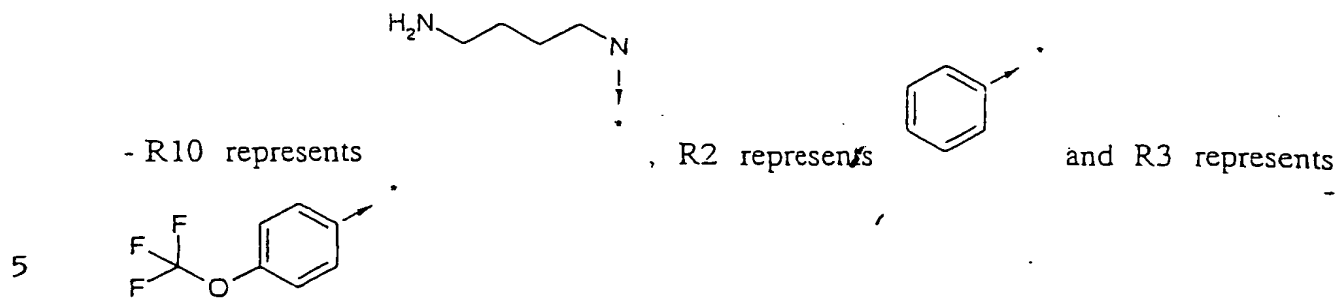
, R2 represents

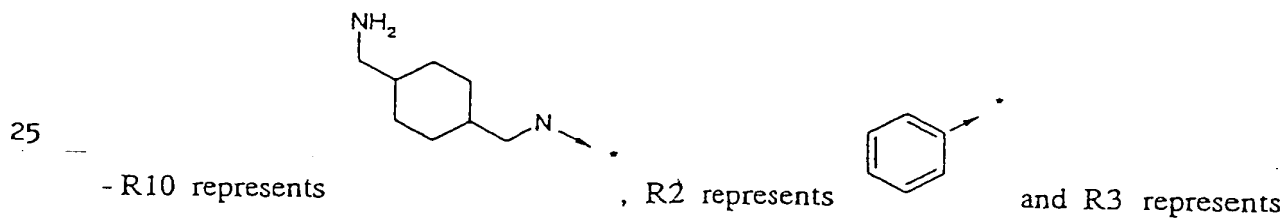
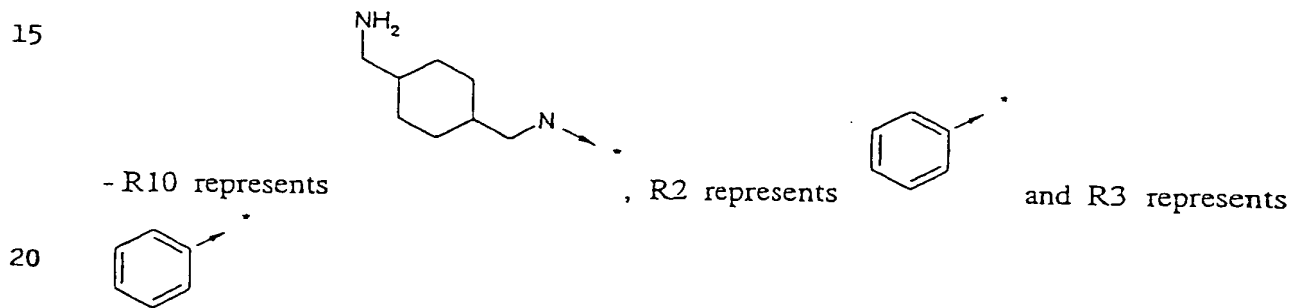
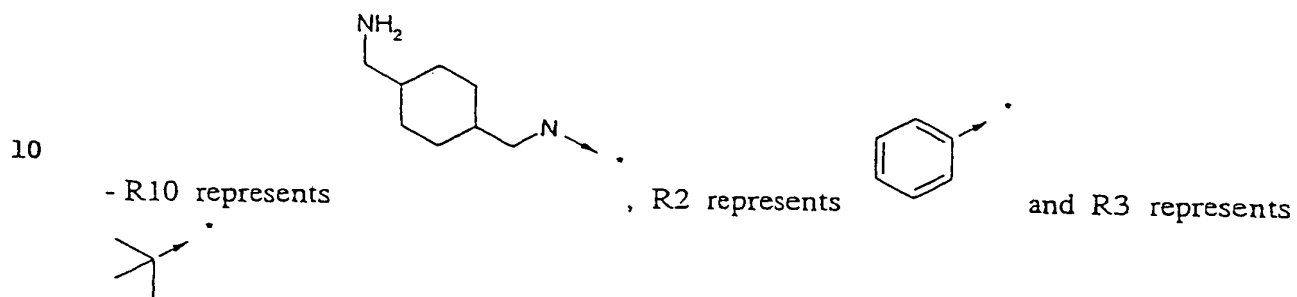
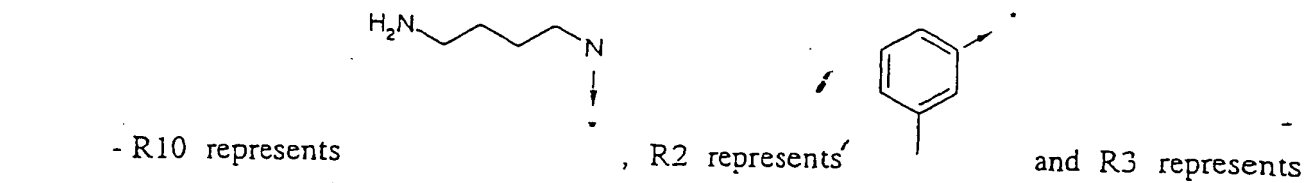


and R3 represents

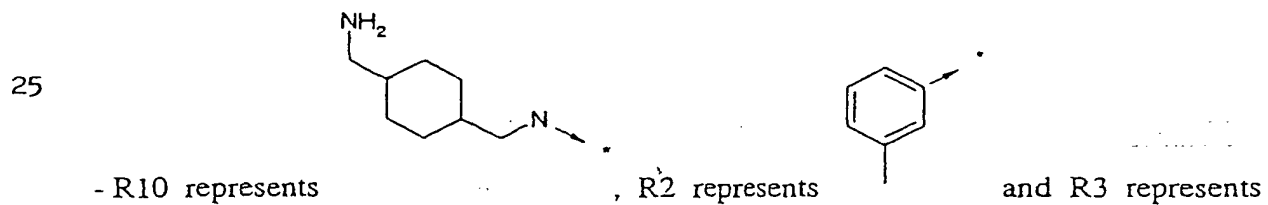
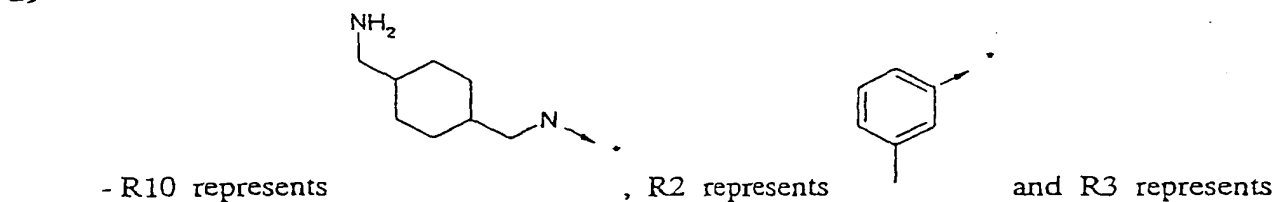
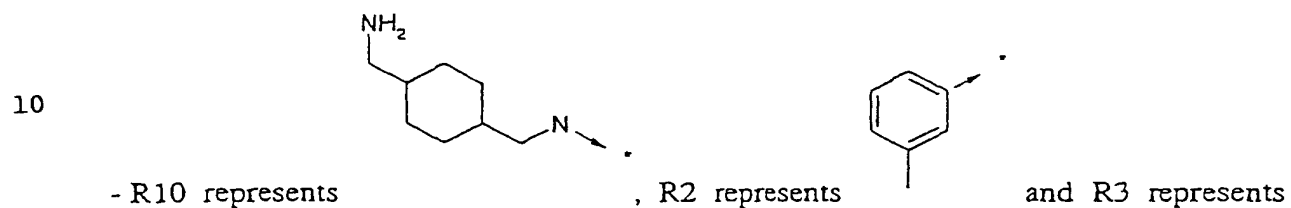
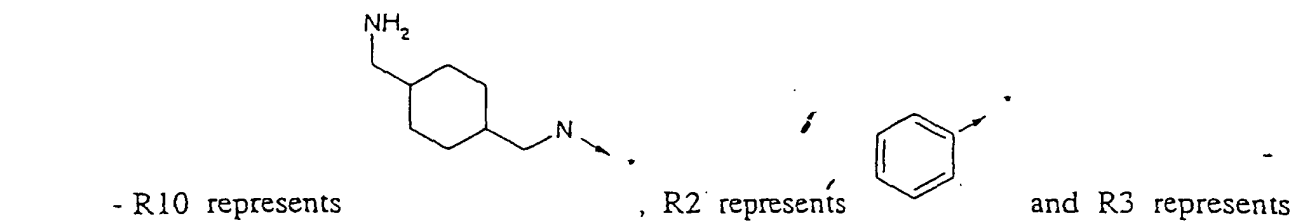
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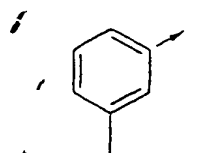
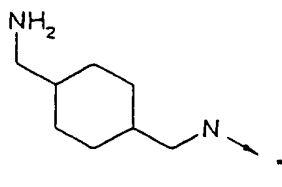
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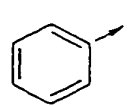
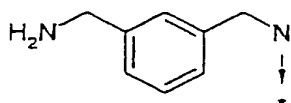
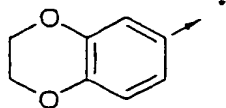


- R10 represents

, R2 represents

and R3 represents

5

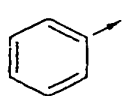
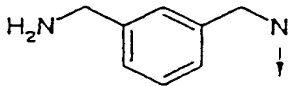
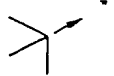


- R10 represents

, R2 represents

and R3 represents

10

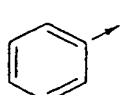
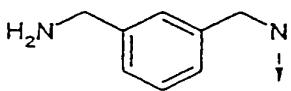
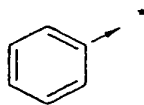


- R10 represents

, R2 represents

and R3 represents

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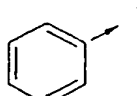
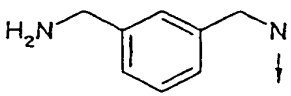
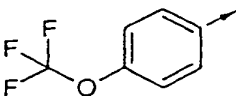


- R10 represents

, R2 represents

and R3 represents

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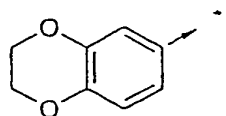


- R10 represents

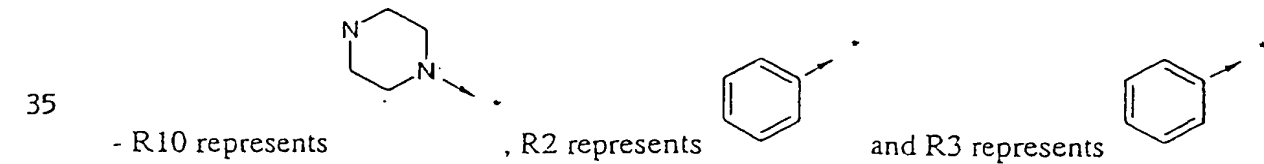
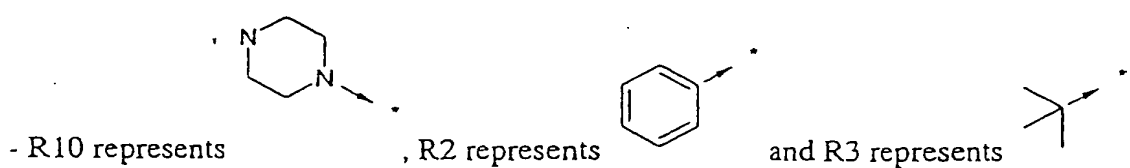
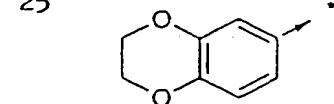
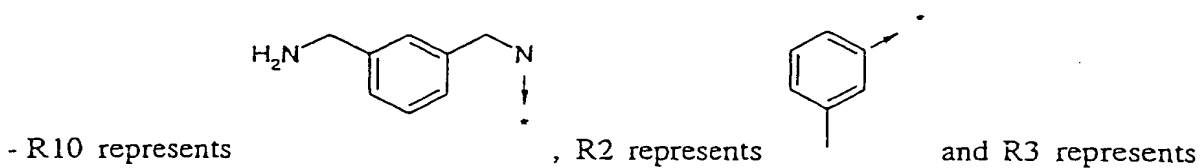
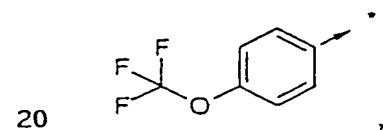
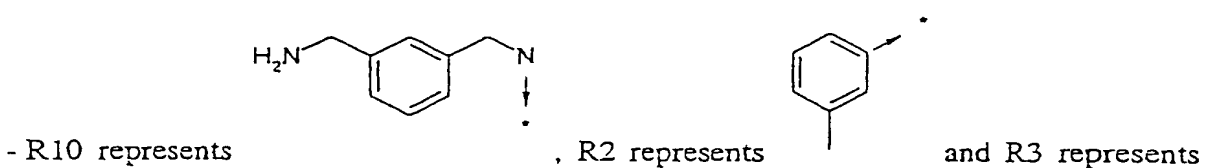
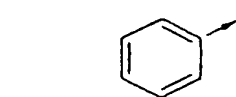
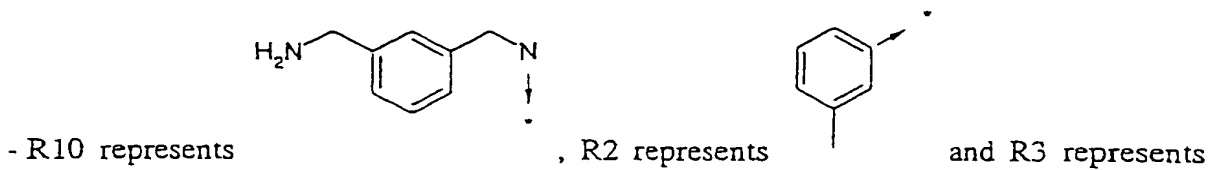
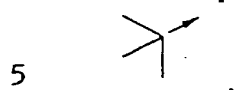
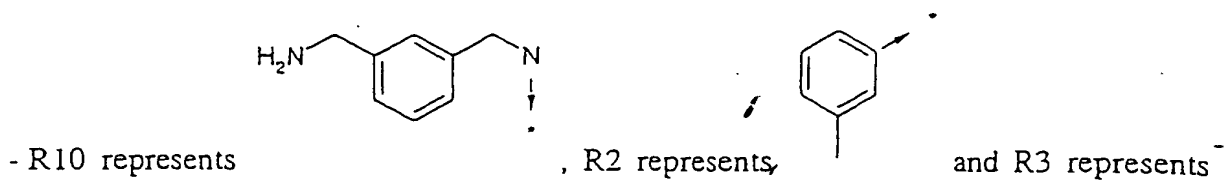
, R2 represents

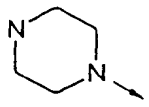
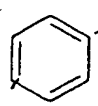
and R3 represents

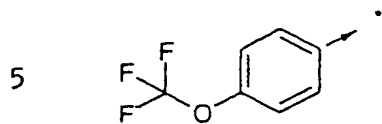
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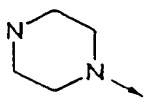
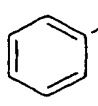


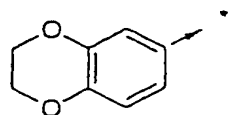
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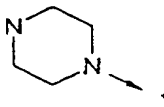
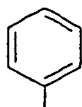



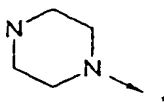
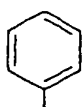
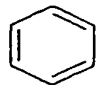
- R10 represents , R2 represents  and R3 represents

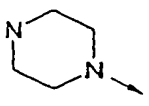
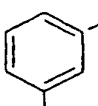


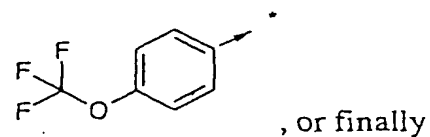
- R10 represents , R2 represents  and R3 represents

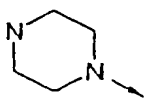
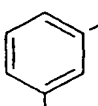


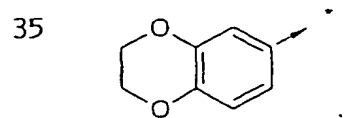
15 - R10 represents , R2 represents  and R3 represents 

20 - R10 represents , R2 represents  and R3 represents 

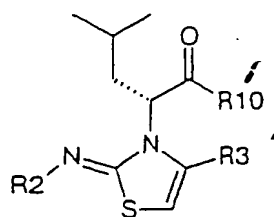
25 - R10 represents , R2 represents  and R3 represents



30 - R10 represents , R2 represents  and R3 represents



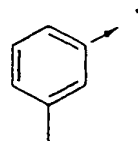
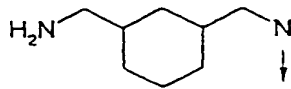
- to formula



(iii)

in which:

10

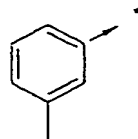
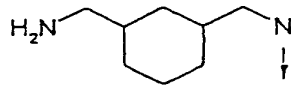
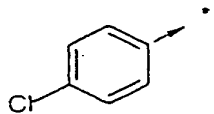


- R10 represents

, R2 represents

and R3 represents

15

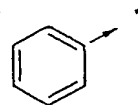
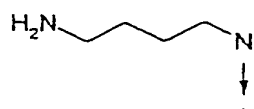
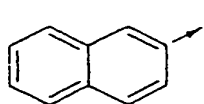


- R10 represents

, R2 represents

and R3 represents

20

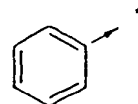
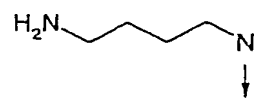
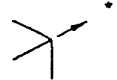


- R10 represents

, R2 represents

and R3 represents

25

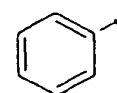


- R10 represents

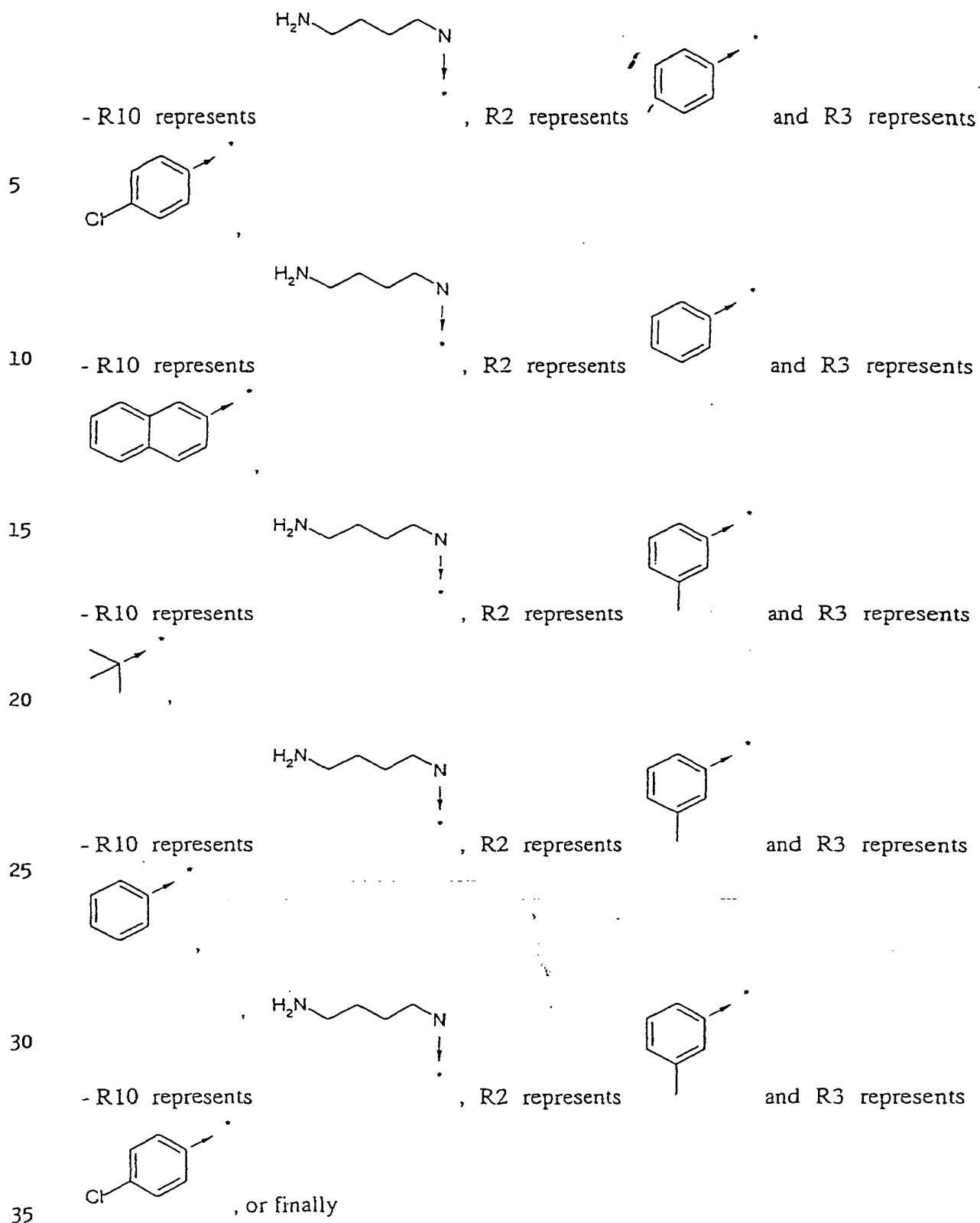
, R2 represents

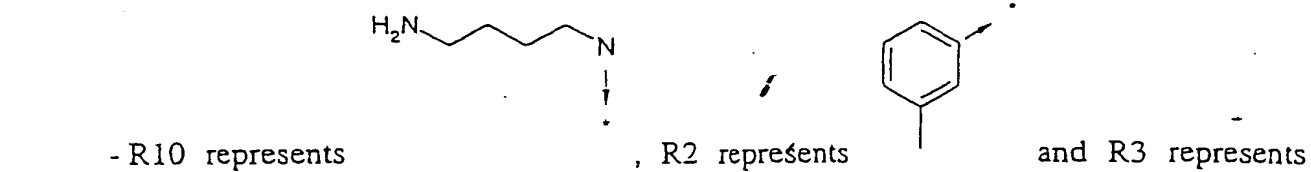
and R3 represents

30



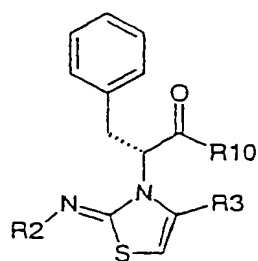
35





• to formula

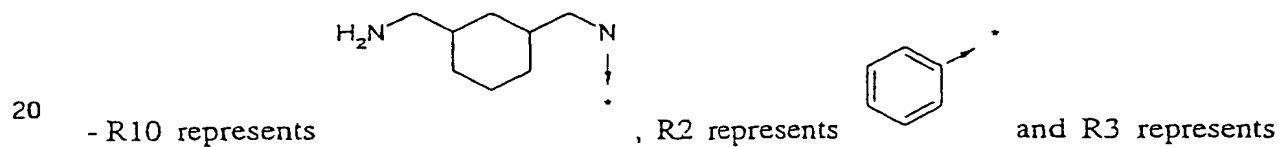
10



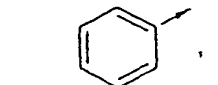
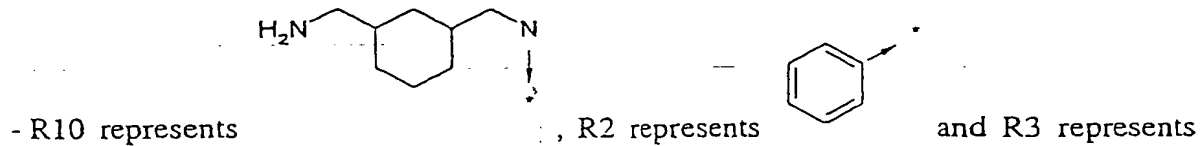
(iv)

15

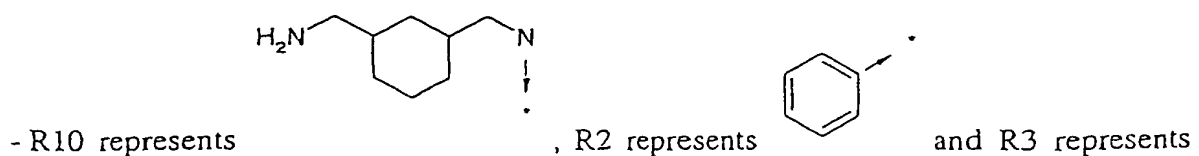
in which:



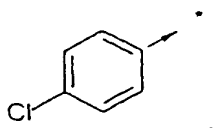
25

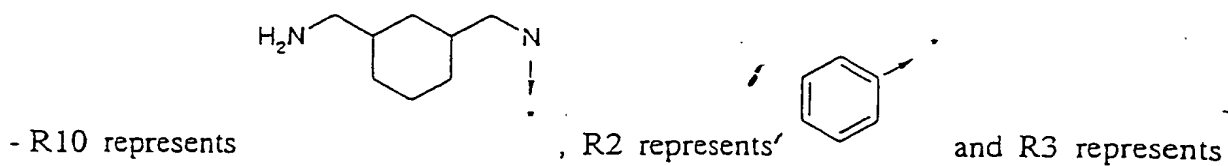


30

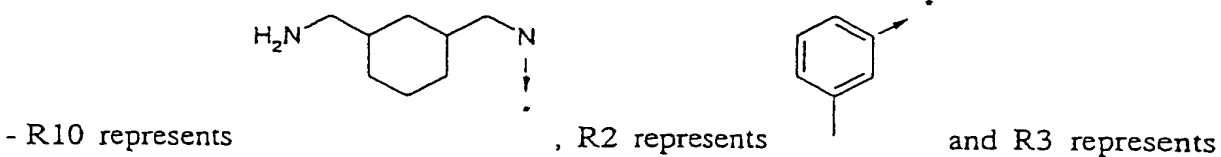
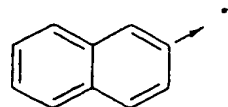


35

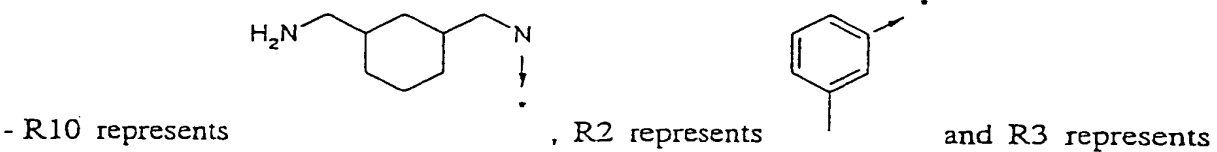




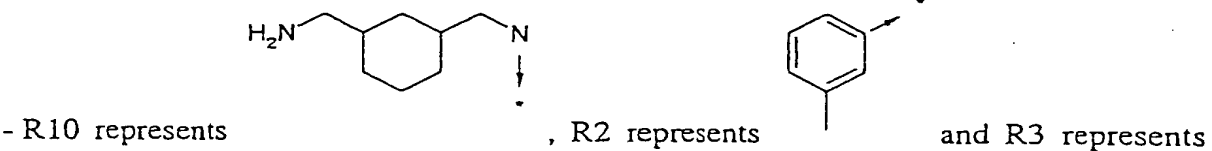
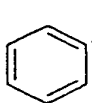
5



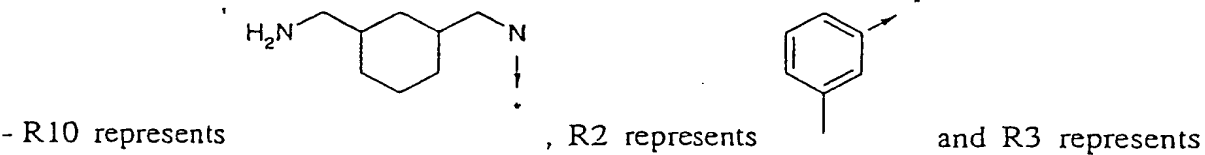
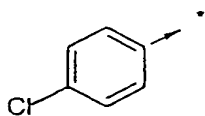
10



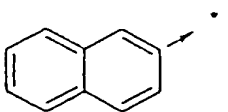
15



25

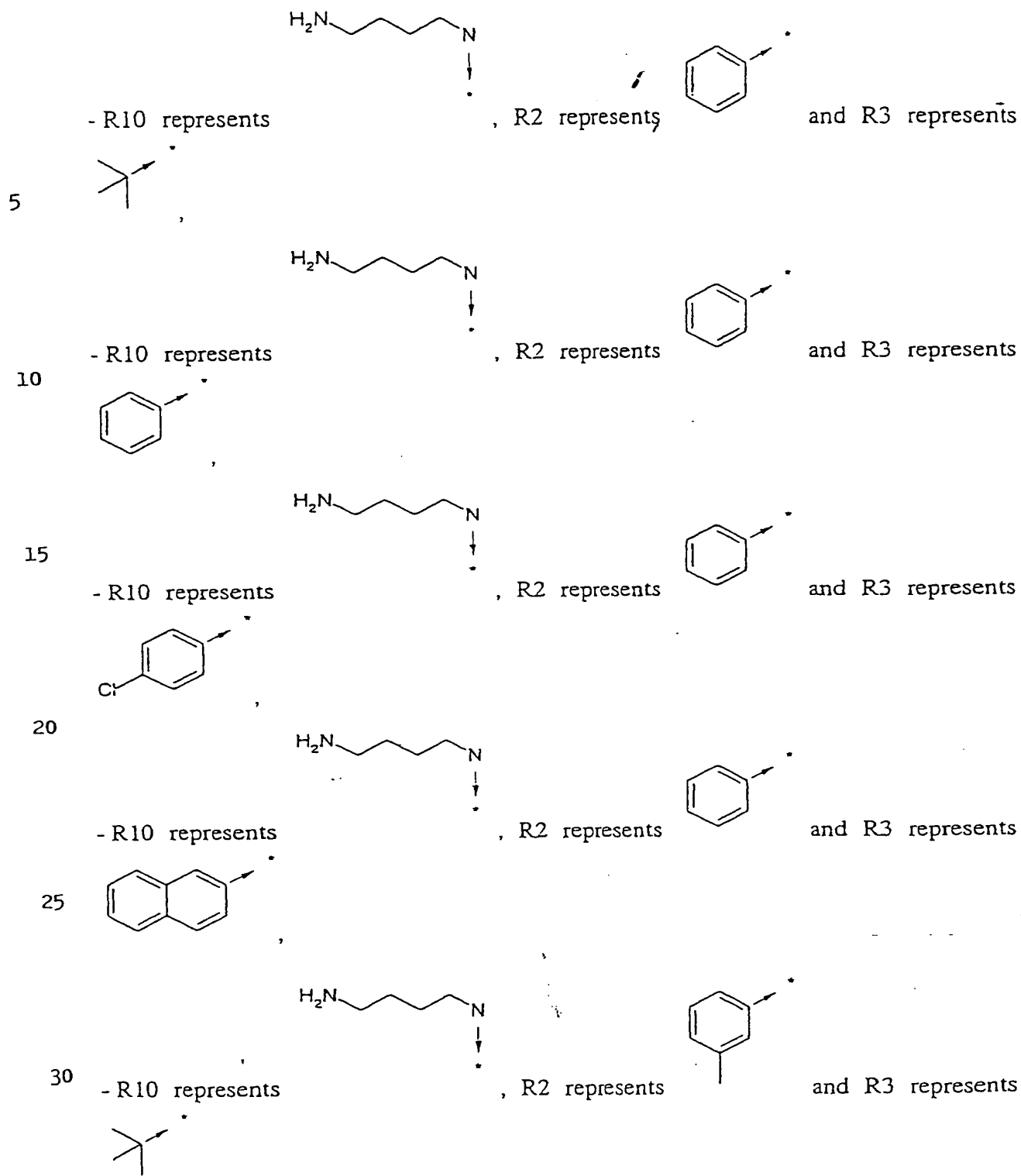


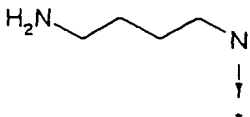
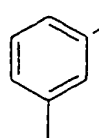
30

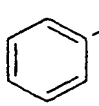
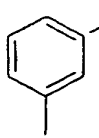


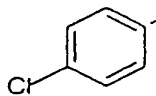
35

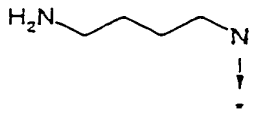
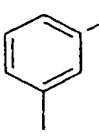




5 - R10 represents  , R2 represents  and R3 represents

10 - R10 represents  , R2 represents  and R3 represents

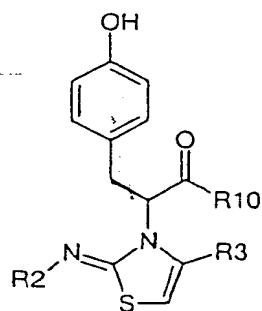
15 - R10 represents  , or finally

20 - R10 represents  , R2 represents  and R3 represents

25 ;

• to formula

25



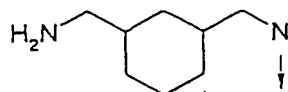
(v)

30

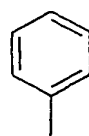
in which:

5

- R10 represents



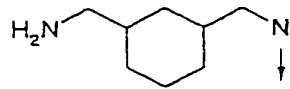
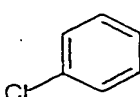
, R2 represents



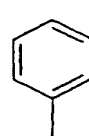
and R3 represents

10

- R10 represents



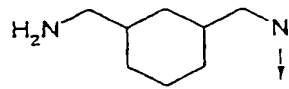
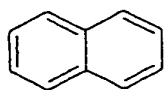
, R2 represents



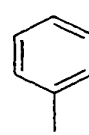
and R3 represents

15

- R10 represents



, R2 represents

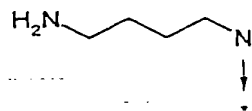


and R3 represents

20

25

- R10 represents



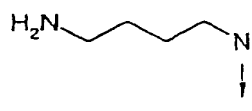
, R2 represents



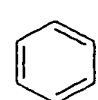
and R3 represents

30

- R10 represents

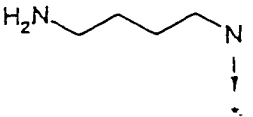
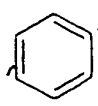


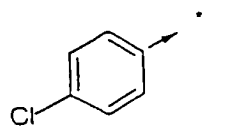
, R2 represents

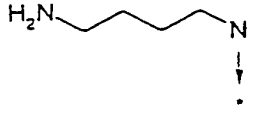
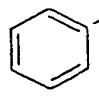


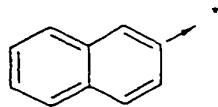
and R3 represents

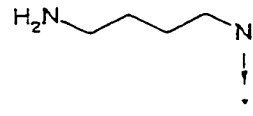
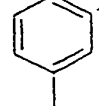
35

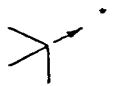
- R10 represents , R2 represents  and R3 represents

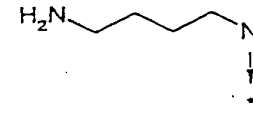
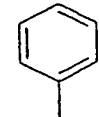


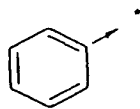
- R10 represents , R2 represents  and R3 represents

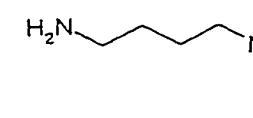
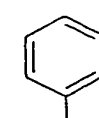


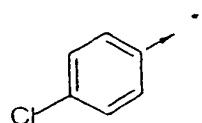
- R10 represents , R2 represents  and R3 represents

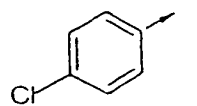


- R10 represents , R2 represents  and R3 represents

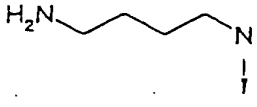
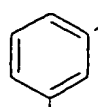


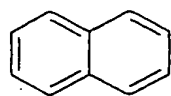
- R10 represents , R2 represents  and R3 represents



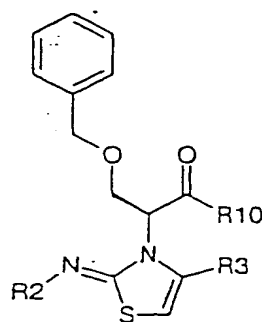
30 , or finally



- R10 represents  , R2 represents  and R3 represents

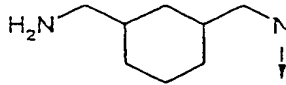



• in formula

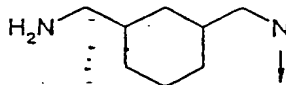



(vi)

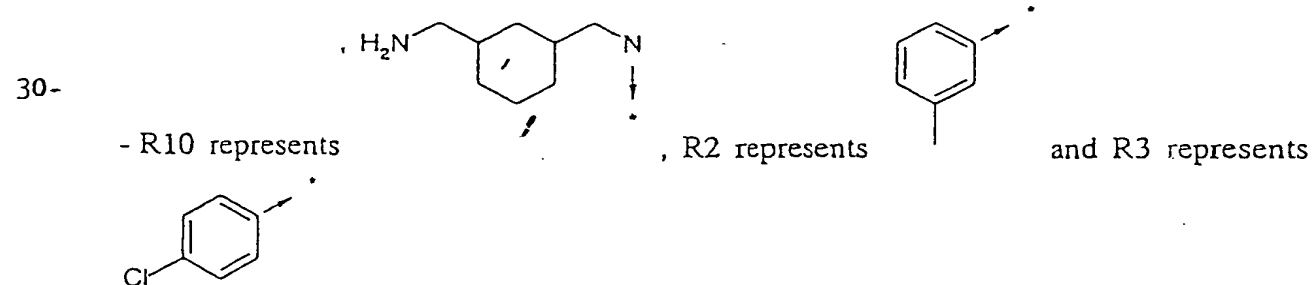
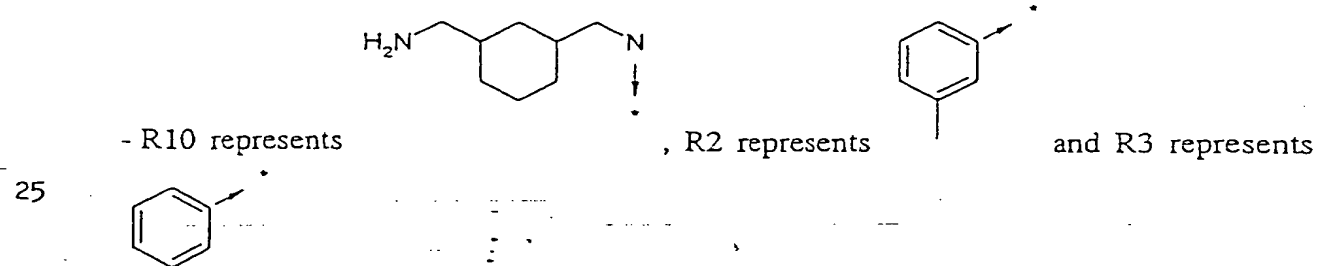
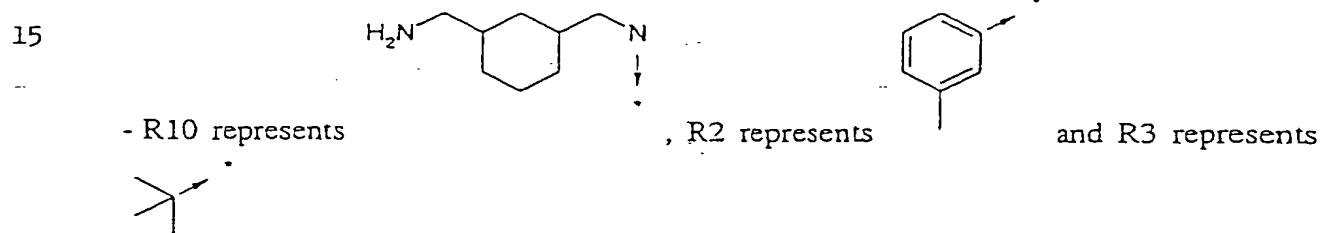
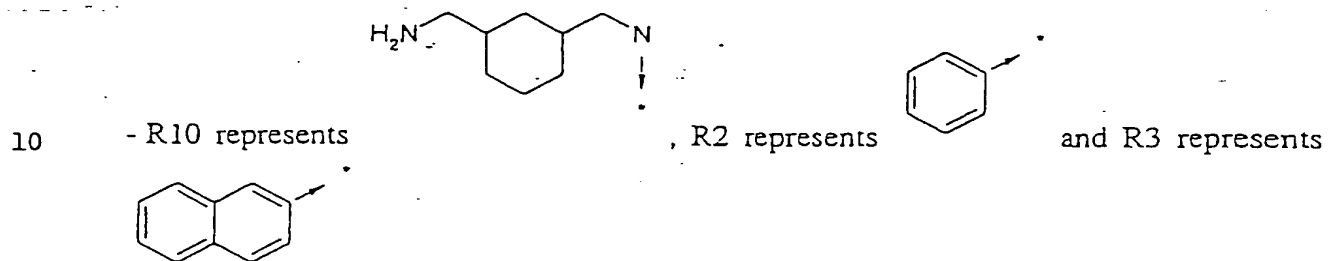
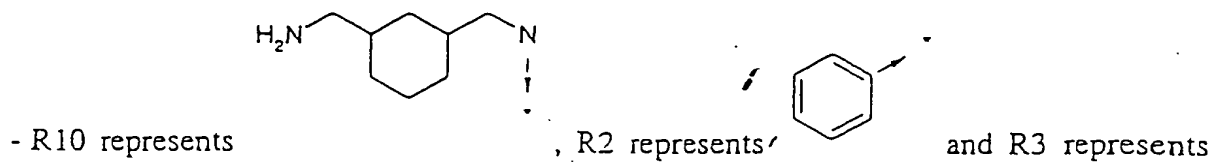
in which:

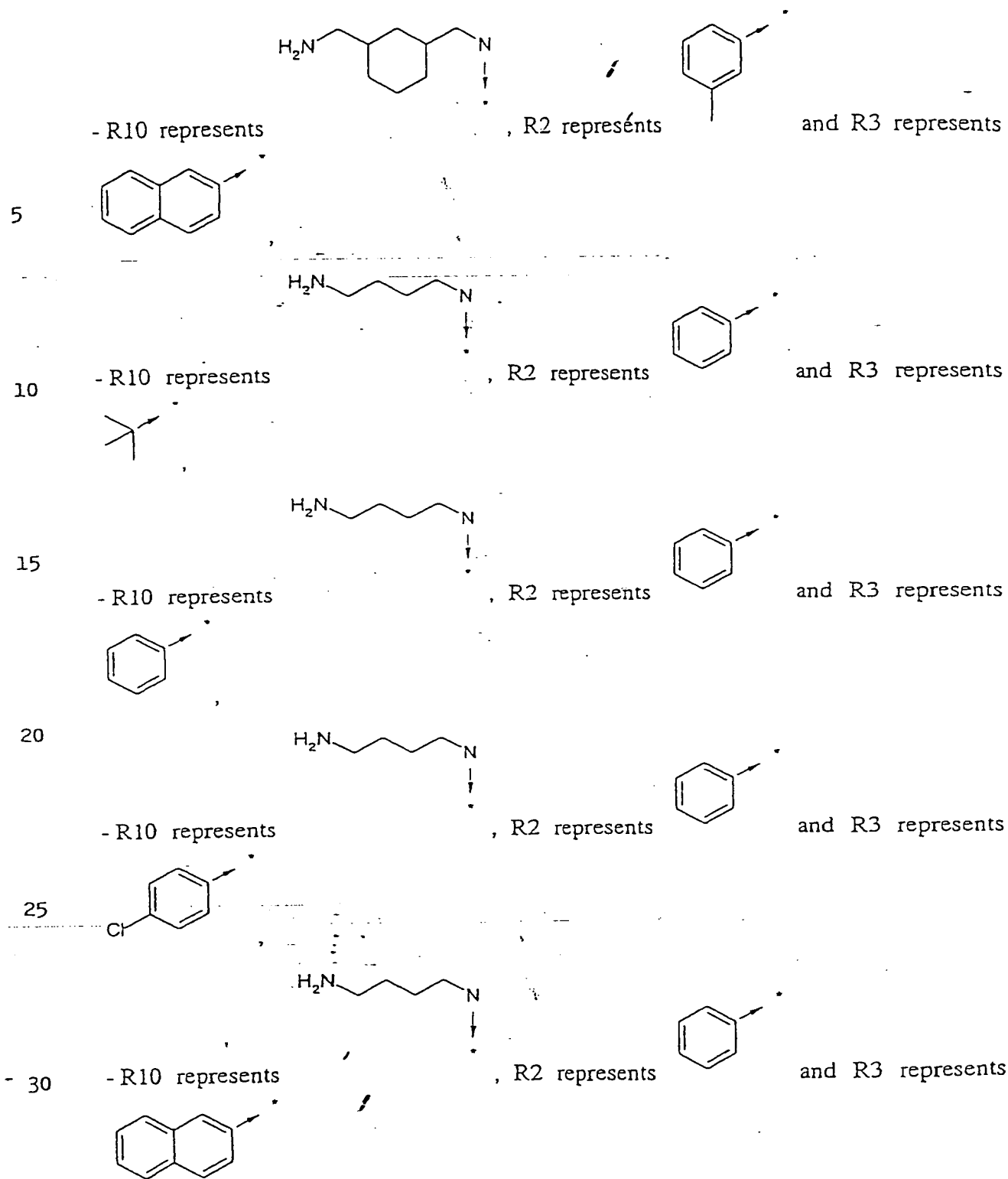
- R10 represents  , R2 represents  and R3 represents



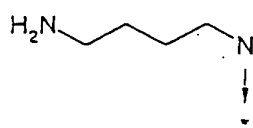
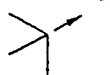
- R10 represents  , R2 represents  and R3 represents



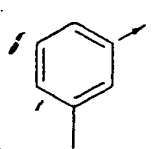




- R10 represents

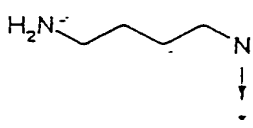
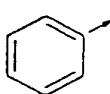


, R2 represents

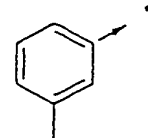


and R3 represents

- R10 represents

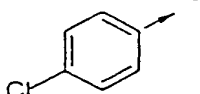


, R2 represents

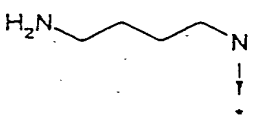


and R3 represents

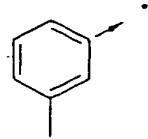
- R10 represents



, or finally

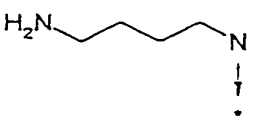
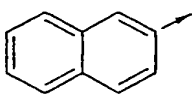


, R2 represents

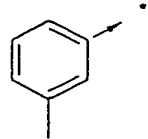


and R3 represents

- R10 represents

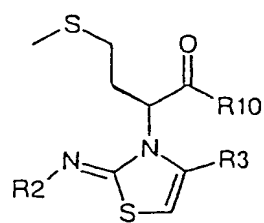


, R2 represents



and R3 represents

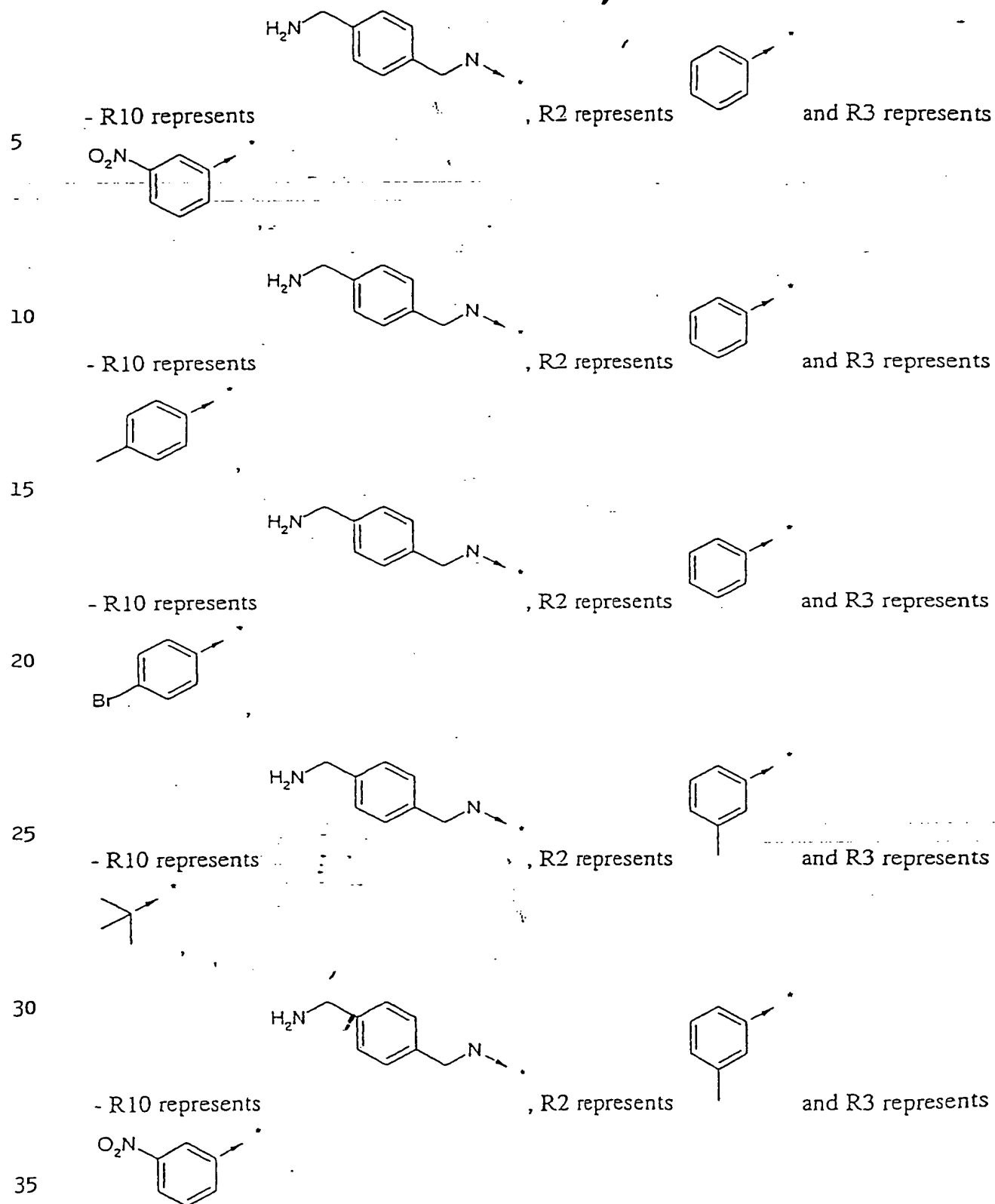
• to formula



(vii)

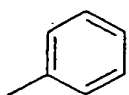


in which:

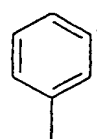


5

- R10 represents



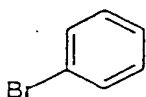
, R2 represents



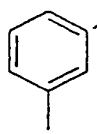
and R3 represents

10

- R10 represents



, R2 represents

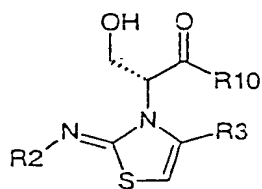


and R3 represents

15

• to formula

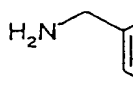
20



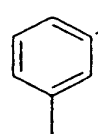
(viii)

25

in which R10 represents



, R2 represents



and R3

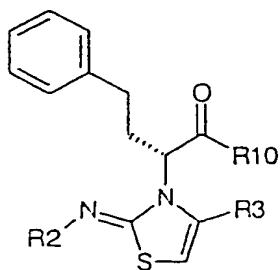
30

represents

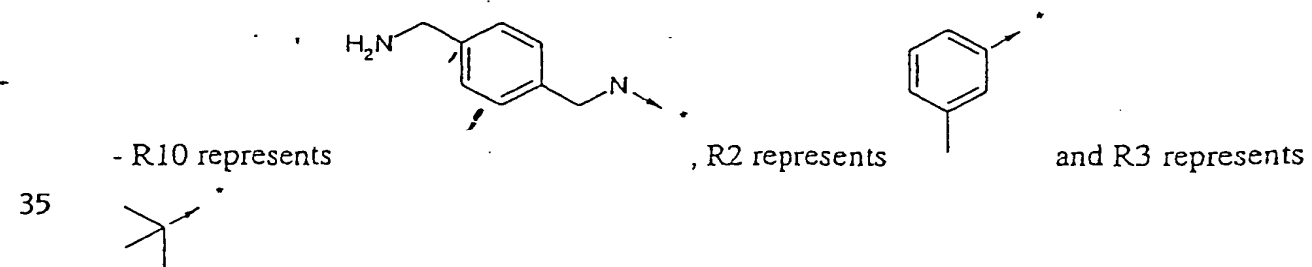
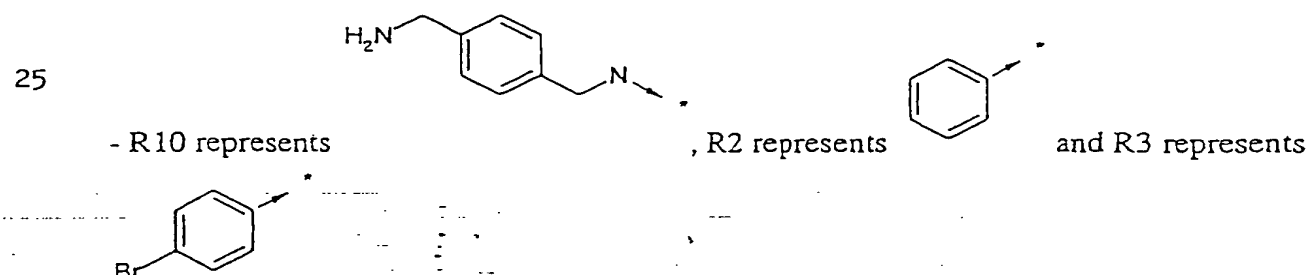
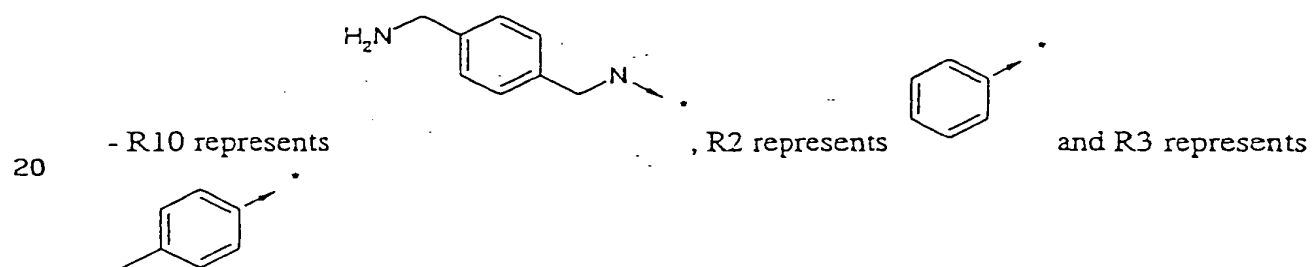
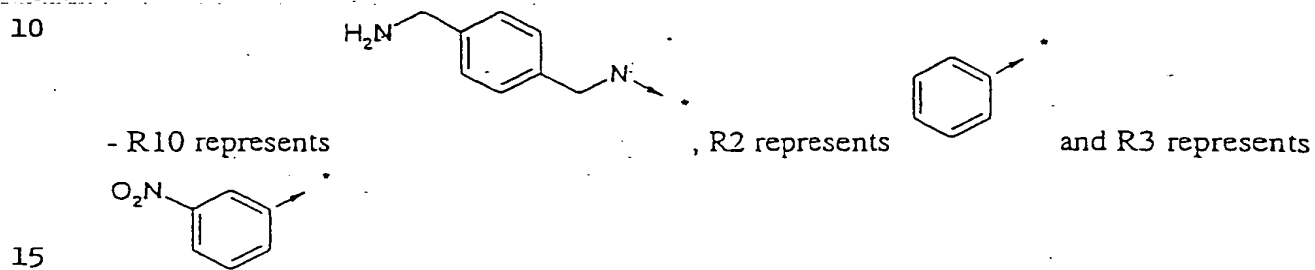
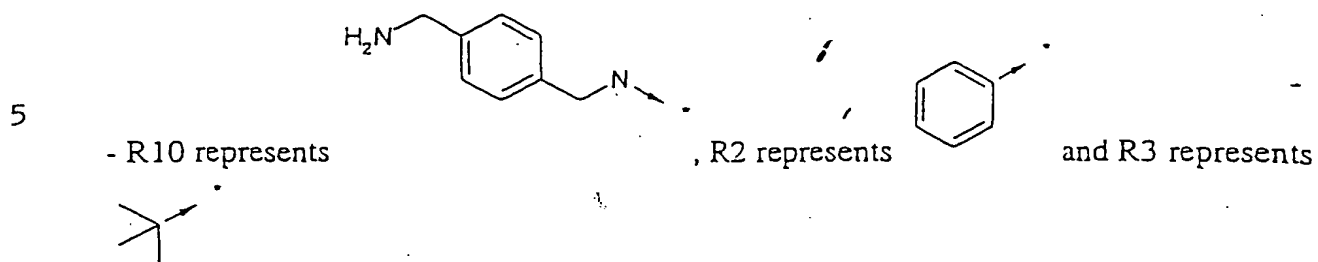


• to formula

35

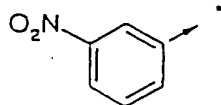


in which:

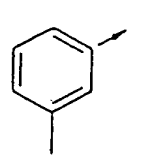


5

- R10 represents



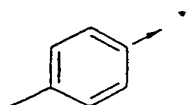
, R2 represents



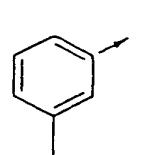
and R3 represents

10

- R10 represents



, R2 represents

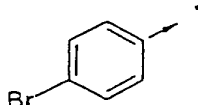


and R3 represents

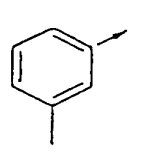
15

, or finally

- R10 represents



, R2 represents

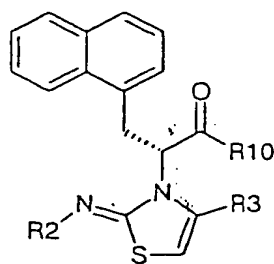


and R3 represents

20

• to formula

25



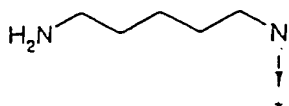
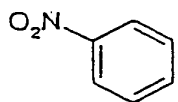
(x)

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in which:

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- R10 represents



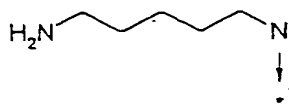
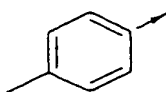
, R2 represents



and R3 represents

10

- R10 represents



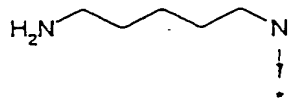
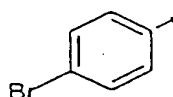
, R2 represents



and R3 represents

15

- R10 represents



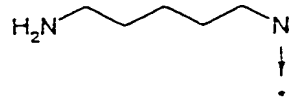
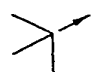
, R2 represents



and R3 represents

20

- R10 represents



, R2 represents

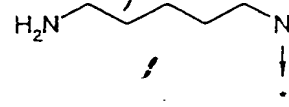
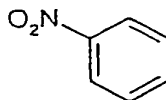


and R3 represents-

25

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- R10 represents



, R2 represents

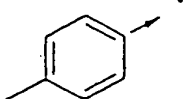


and R3 represents

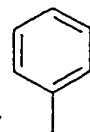
35

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- R10 represents



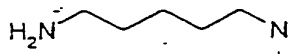
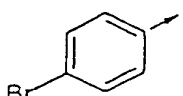
, R2 represents



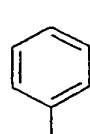
and R3 represents

10

- R10 represents



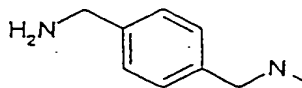
, R2 represents



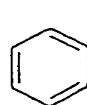
and R3 represents

15

- R10 represents



, R2 represents

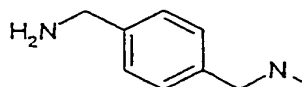
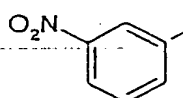


and R3 represents

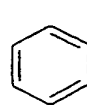
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- R10 represents



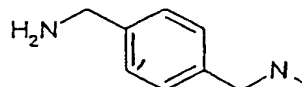
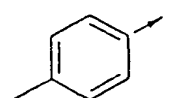
, R2 represents



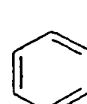
and R3 represents

30

- R10 represents

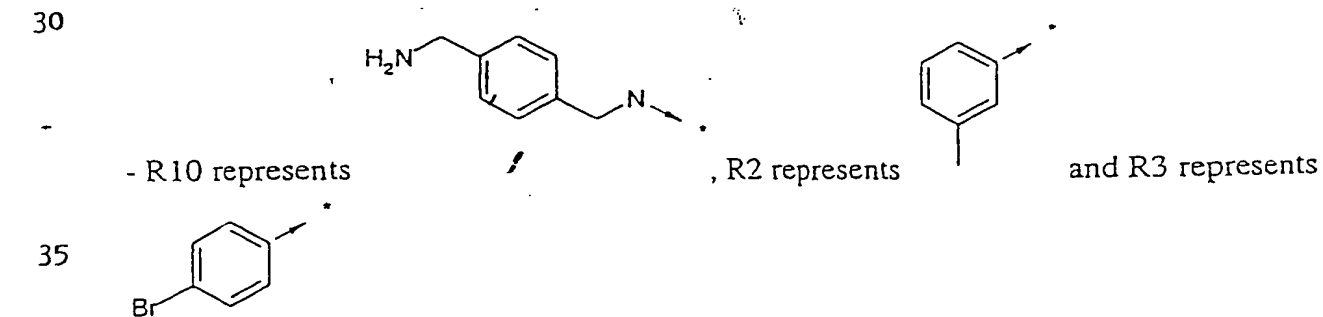
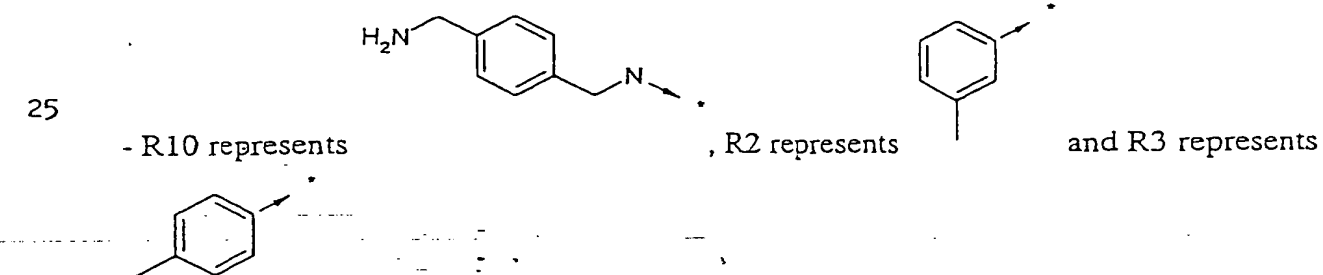
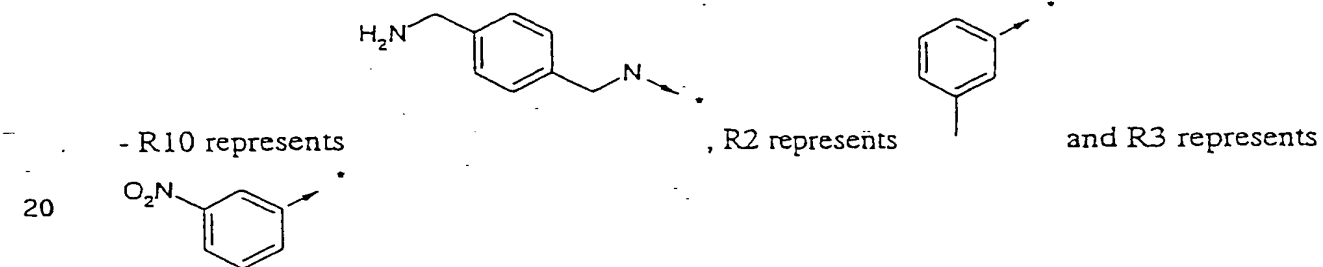
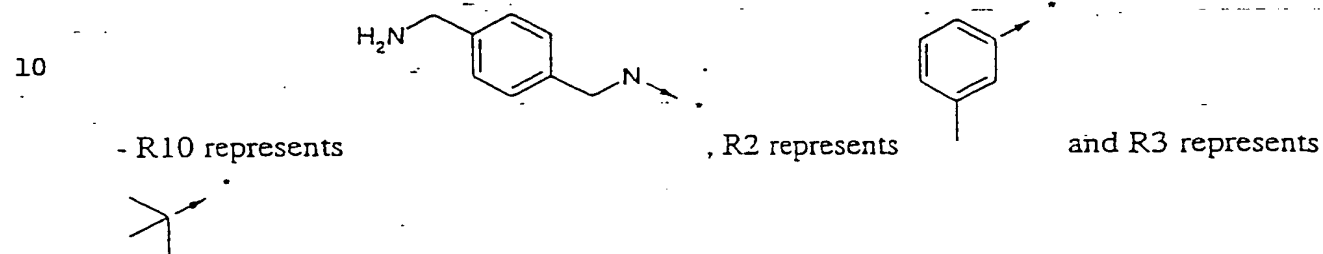
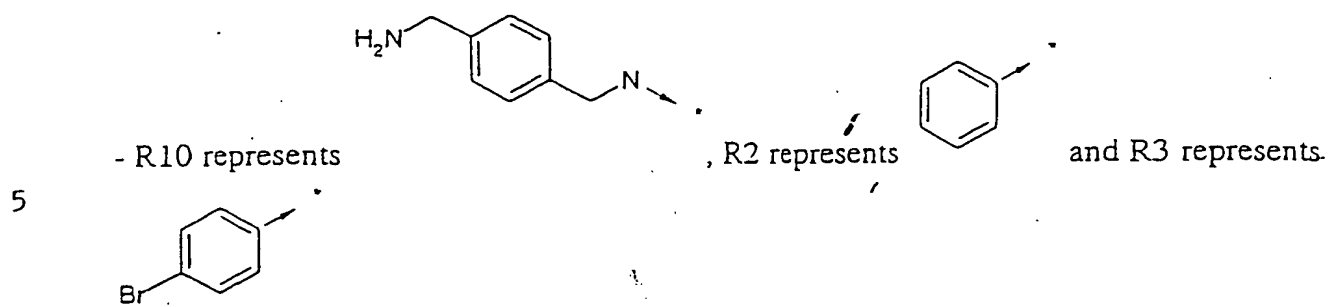


, R2 represents



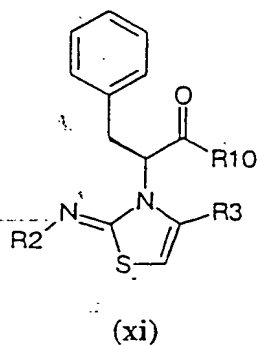
and R3 represents

35



• to formula

5

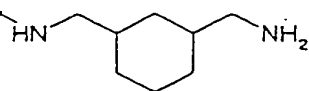


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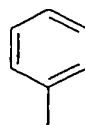
in which:

15

- R10 represents



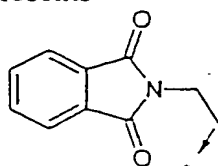
, R2 represents



and R3

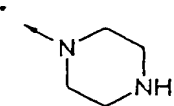
20

represents



25

- R10 represents



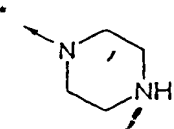
, R2 represents



and R3 represents

30

- R10 represents

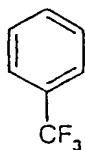


, R2 represents



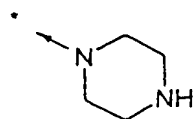
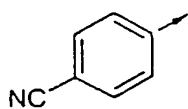
and R3 represents

35

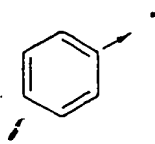




- R10 represents

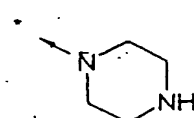
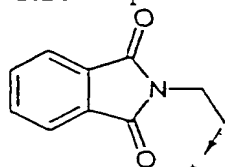


R2 represents

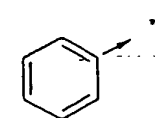


and R3 represents

- R10 represents

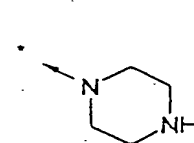
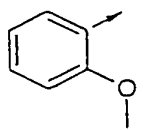


R2 represents

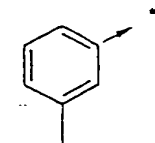


and R3 represents

- R10 represents

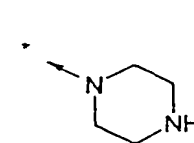
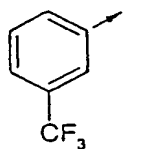


R2 represents

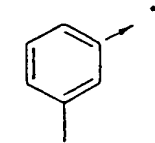


and R3 represents

- R10 represents

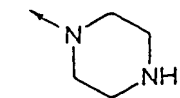


R2 represents

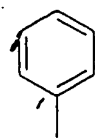


and R3 represents


5 - R10 represents



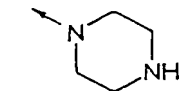
, R2 represents



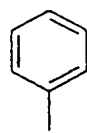
and R3 represents

NC-, or finally

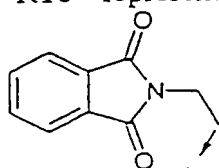
10 - R10 represents



, R2 represents

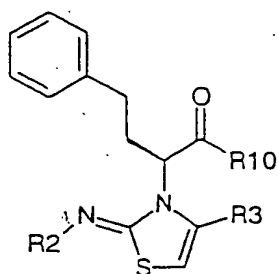


and R3 represents



- in formula

5



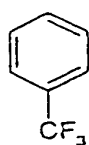
(xii)

10

in which:

15

- R10 represents



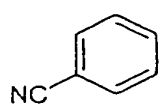
, R2 represents



and R3 represents

20

- R10 represents



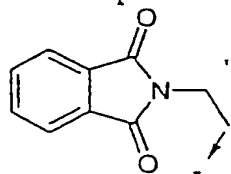
, R2 represents



and R3 represents

25

- R10 represents



, R2 represents



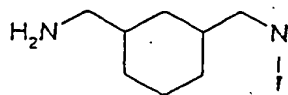
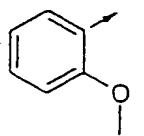
and R3 represents

30

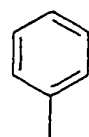
35

5

- R10 represents



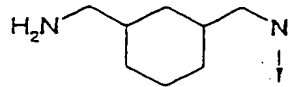
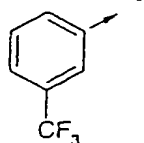
, R2 represents



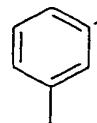
and R3 represents

10

- R10 represents



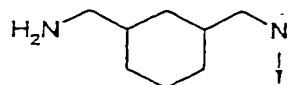
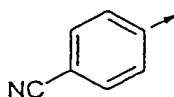
, R2 represents



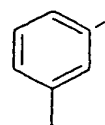
and R3 represents

15

- R10 represents



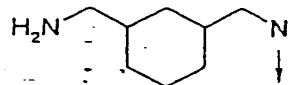
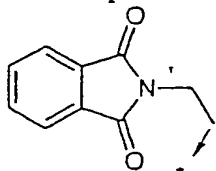
, R2 represents



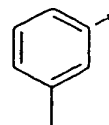
and R3 represents

25

- R10 represents



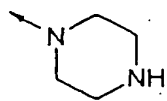
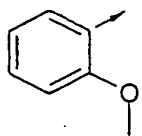
, R2 represents



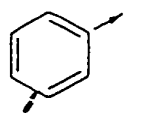
and R3 represents

35

5 - R10 represents



, R2 represents

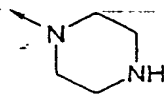
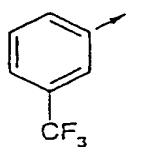


and R3 represents

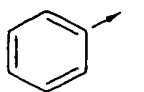
5

10

- R10 represents



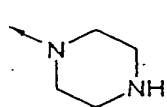
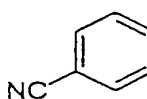
, R2 represents



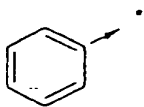
and R3 represents

15

20 - R10 represents



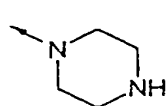
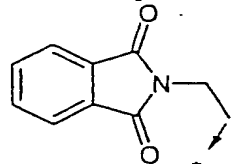
, R2 represents



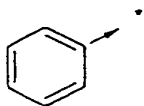
and R3 represents

20

25 - R10 represents



, R2 represents

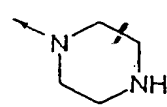
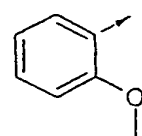


and R3 represents

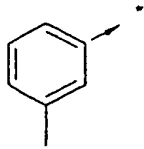
25

30

35 - R10 represents



, R2 represents

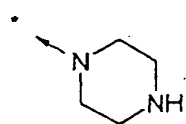
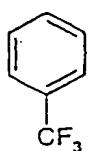


and R3 represents

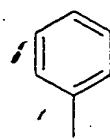
35

5

- R10 represents



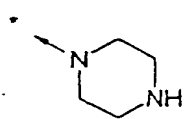
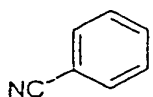
, R2 represents



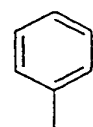
and R3 represents

10

- R10 represents



, R2 represents



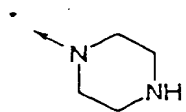
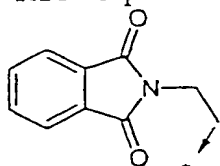
and R3 represents

15

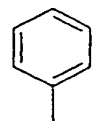
, or finally

20

- R10 represents



, R2 represents

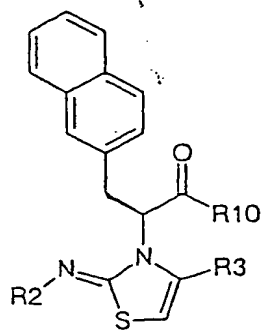


and R3 represents

25

to formula

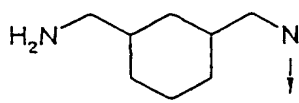
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(xiii)

in which:

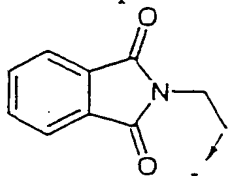


- R10 represents

, R2 represents,

and R3 represents

5



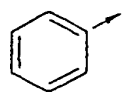
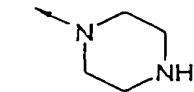
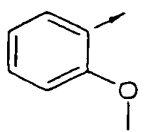
10

- R10 represents

, R2 represents

and R3 represents

15

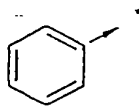
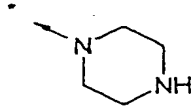
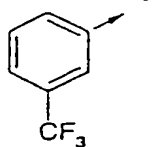


20

- R10 represents

, R2 represents

and R3 represents



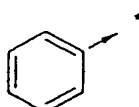
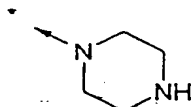
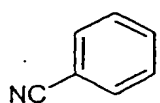
25

- R10 represents

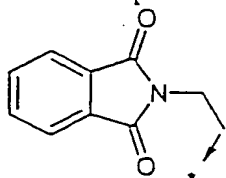
, R2 represents

and R3 represents

30



- R10 represents

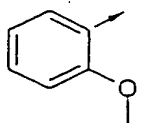


, R2 represents

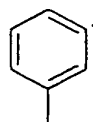


and R3 represents

- R10 represents

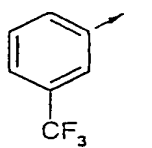


, R2 represents

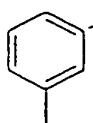


and R3 represents

- R10 represents

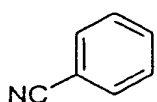


, R2 represents

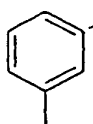


and R3 represents

- R10 represents



, R2 represents



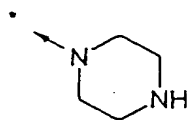
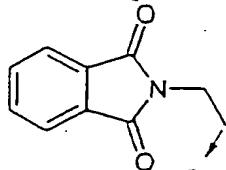
and R3 represents

, or finally

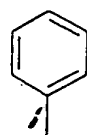


5

- R10 represents



, R2 represents

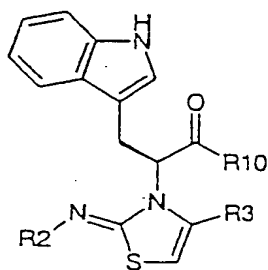


and R3 represents

10

• to formula

15



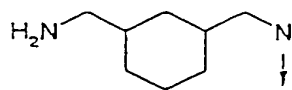
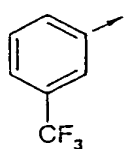
(xiv)

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in which:

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- R10 represents



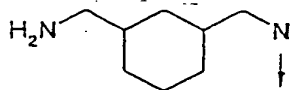
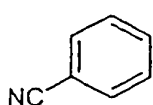
, R2 represents



and R3 represents

30

- R10 represents

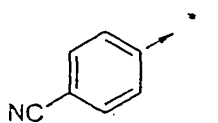
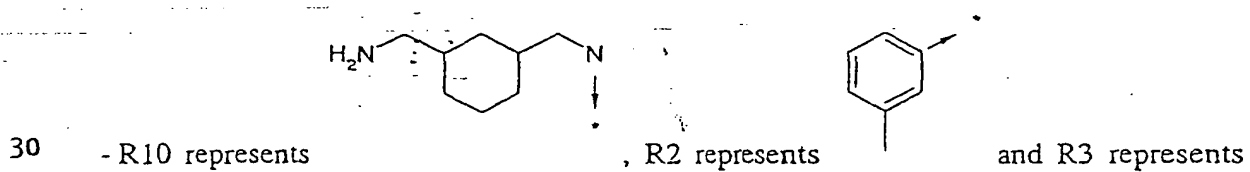
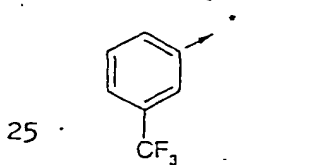
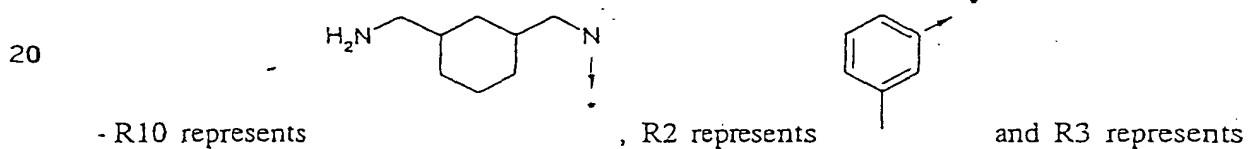
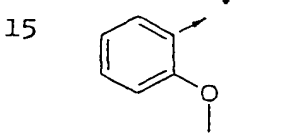
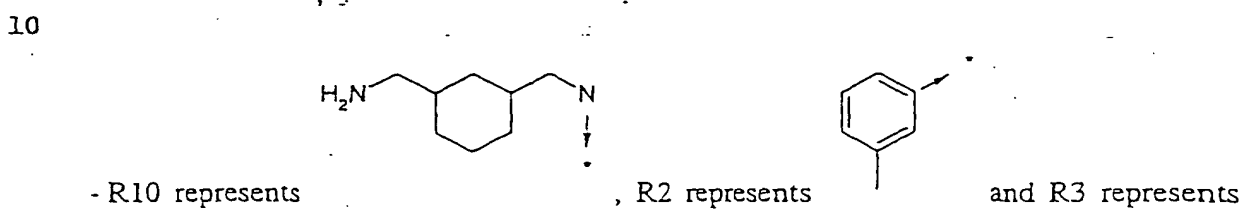
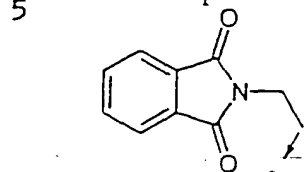
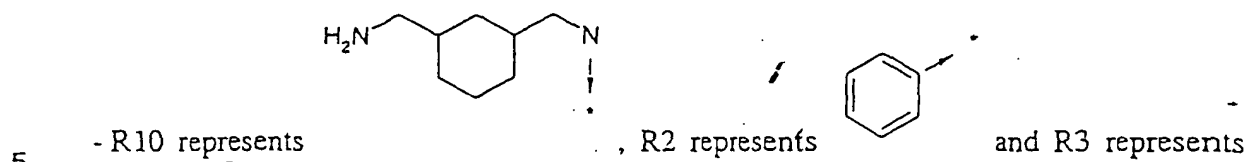


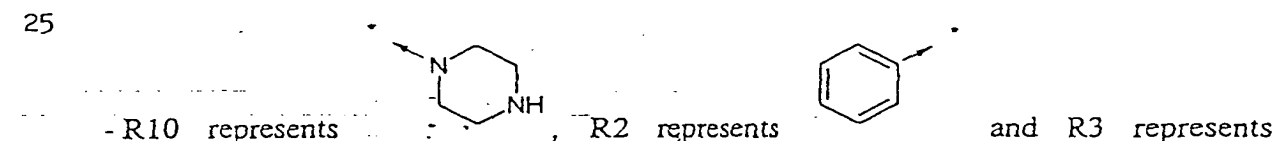
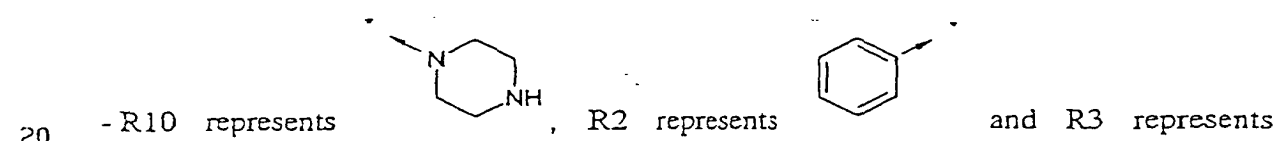
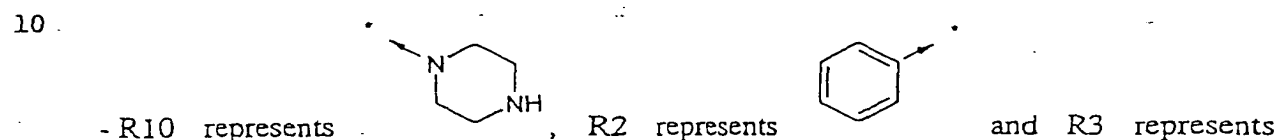
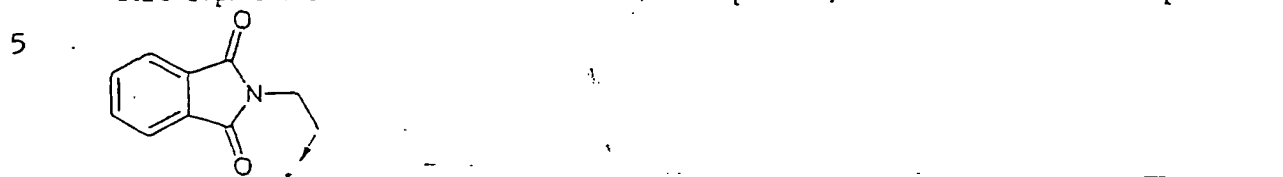
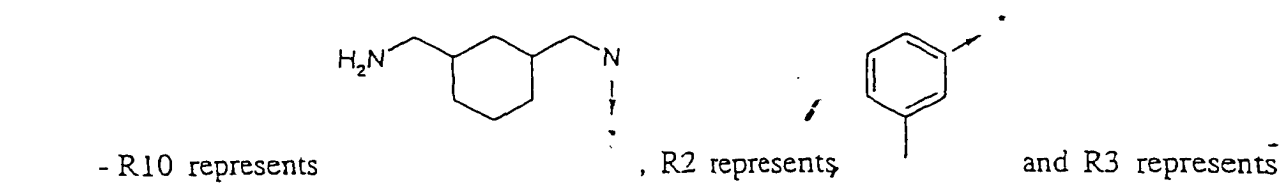
, R2 represents

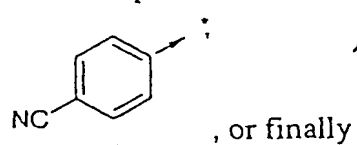
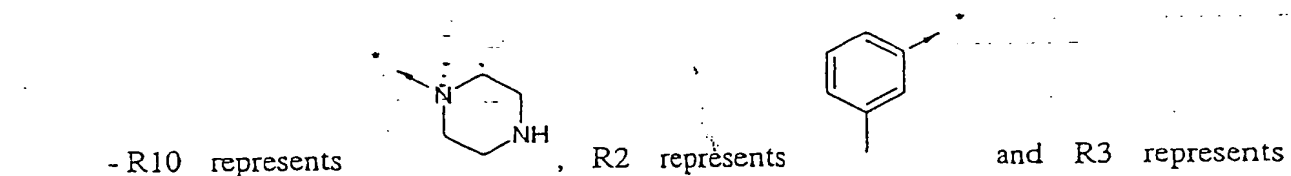
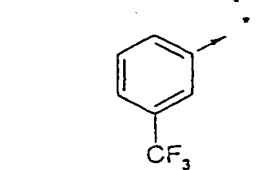
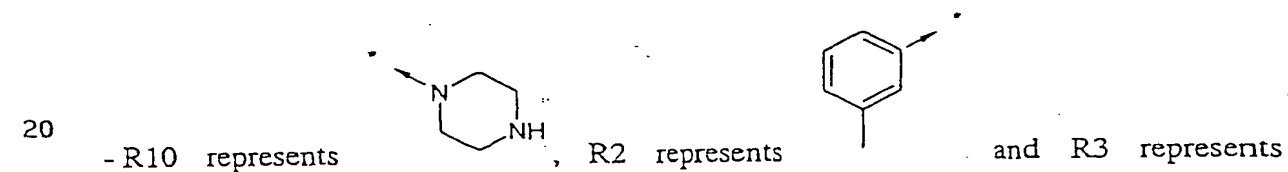
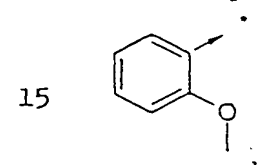
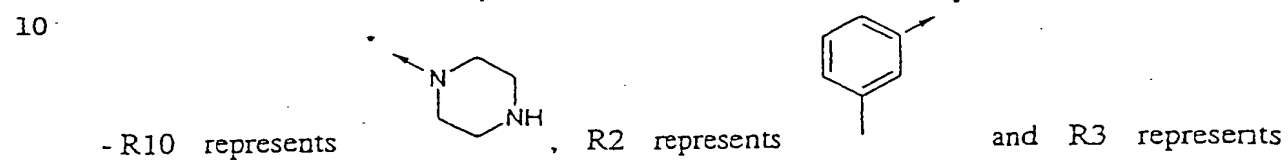
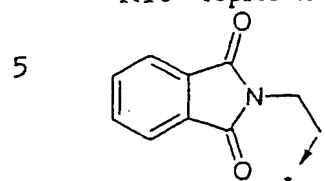
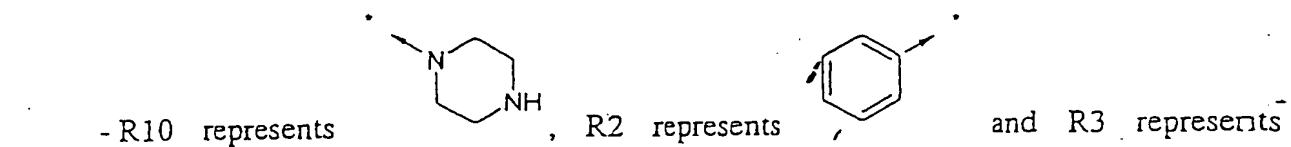


and R3 represents

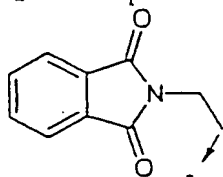
35



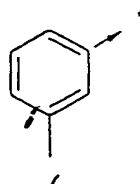




- R10 represents



, R2 represents

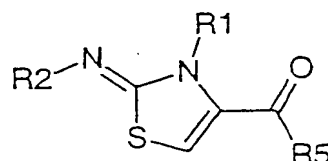


and R3 represents

5

10

• or finally to formula



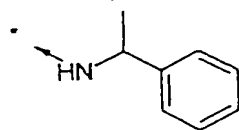
(xv)

15

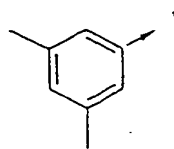
in which:

20

- R1 represents



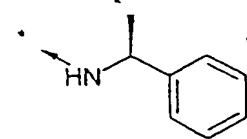
, R2 represents



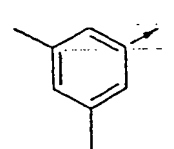
and R5 represents

25

- R1 represents



, R2 represents



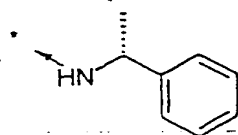
and R5 represents

30

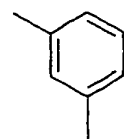
35

5

- R1 represents



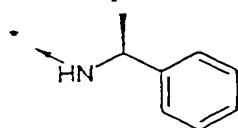
, R2 represents



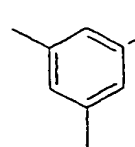
and R5 represents

10

- R1 represents



, R2 represents

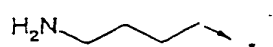
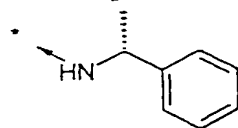


and R5 represents

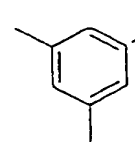
15

20

- R1 represents



, R2 represents

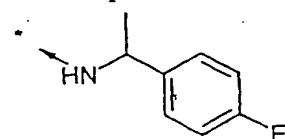


and R5 represents

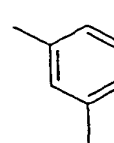
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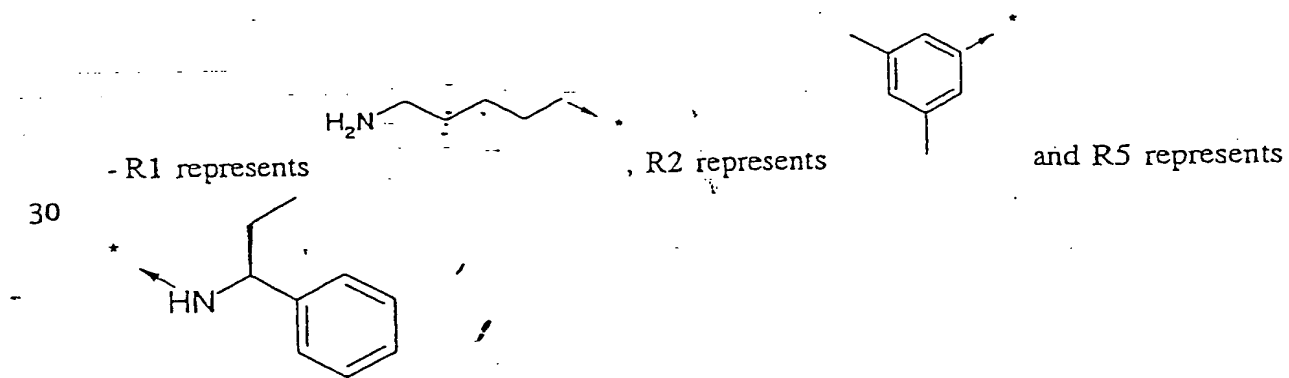
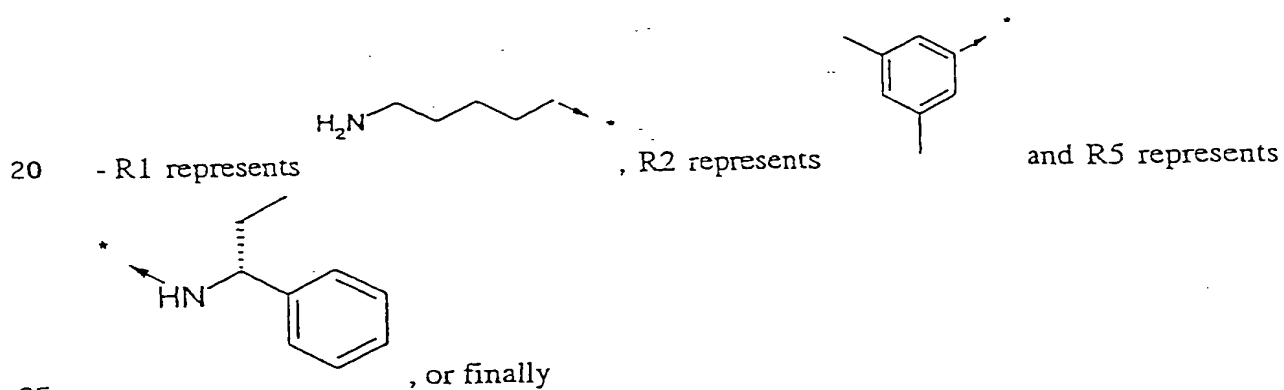
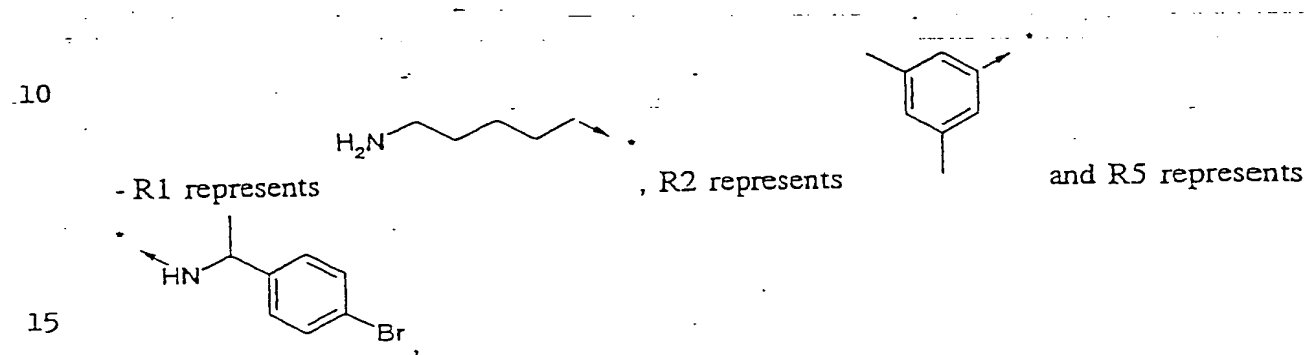
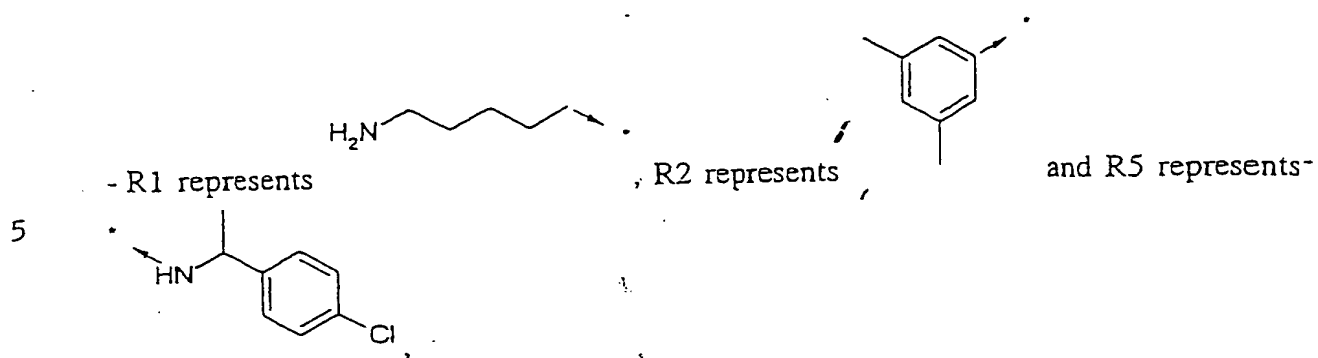
- R1 represents



, R2 represents

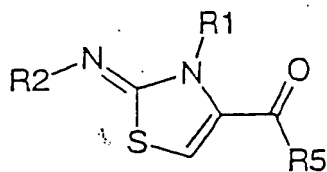


and R5 represents



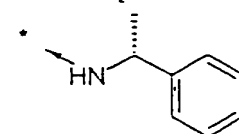
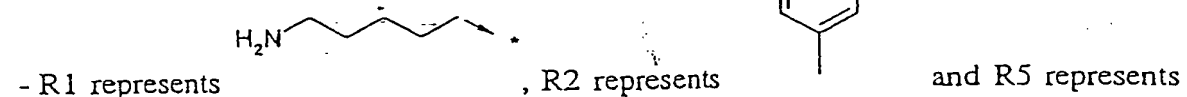
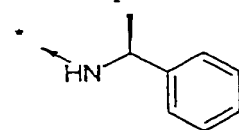
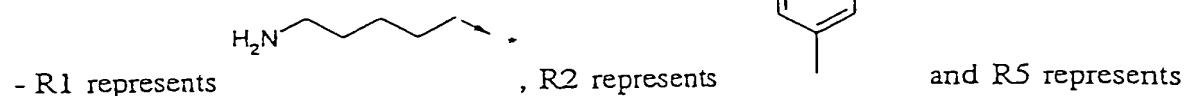
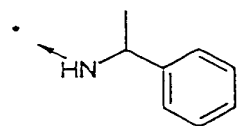
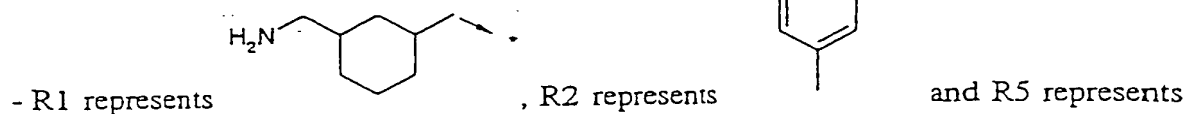
35 or a salt of one of these compounds.

Even more preferentially, the invention relates to a compound characterized in that it corresponds to the formula

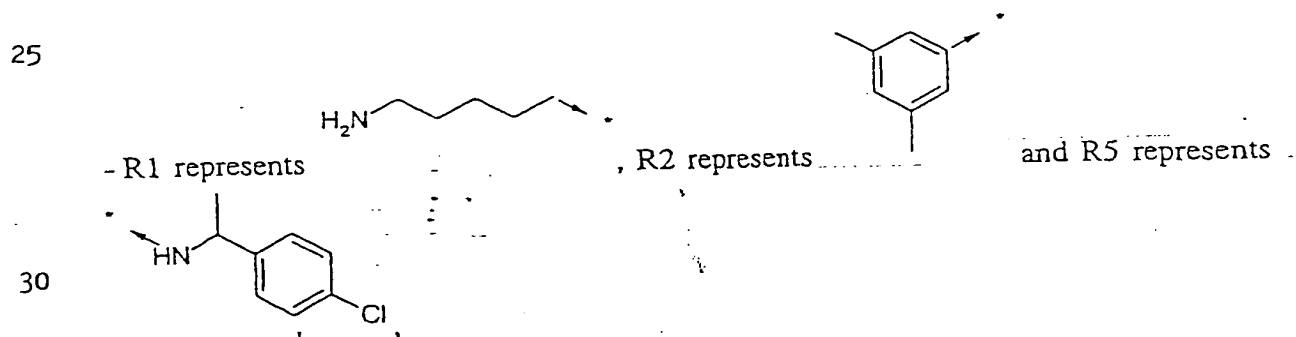
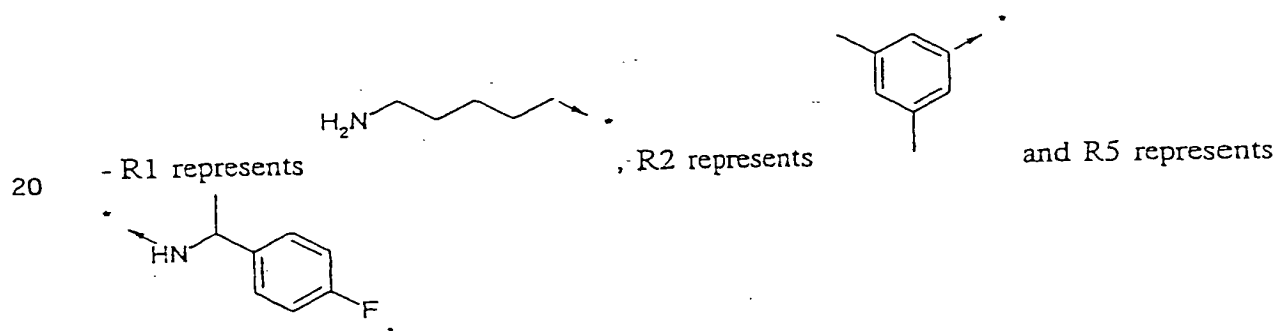
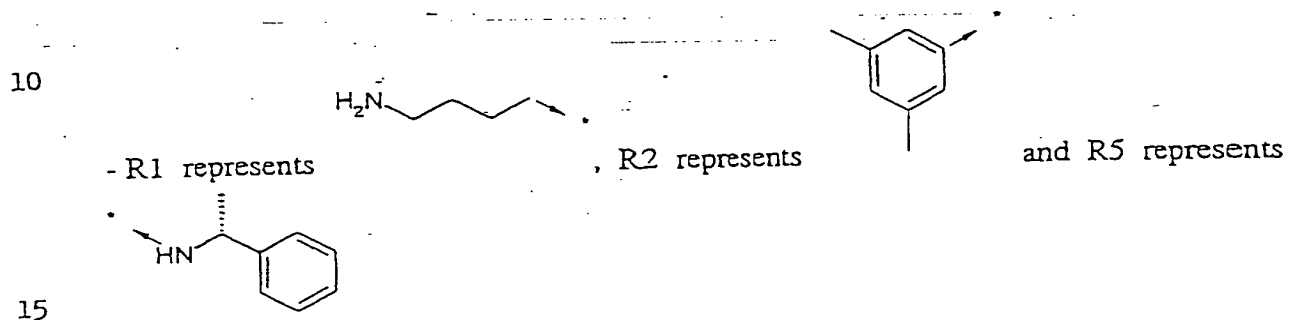
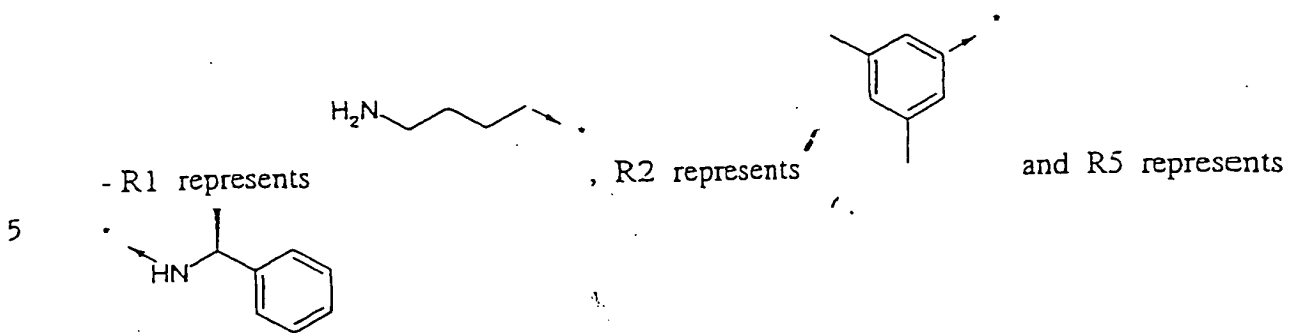


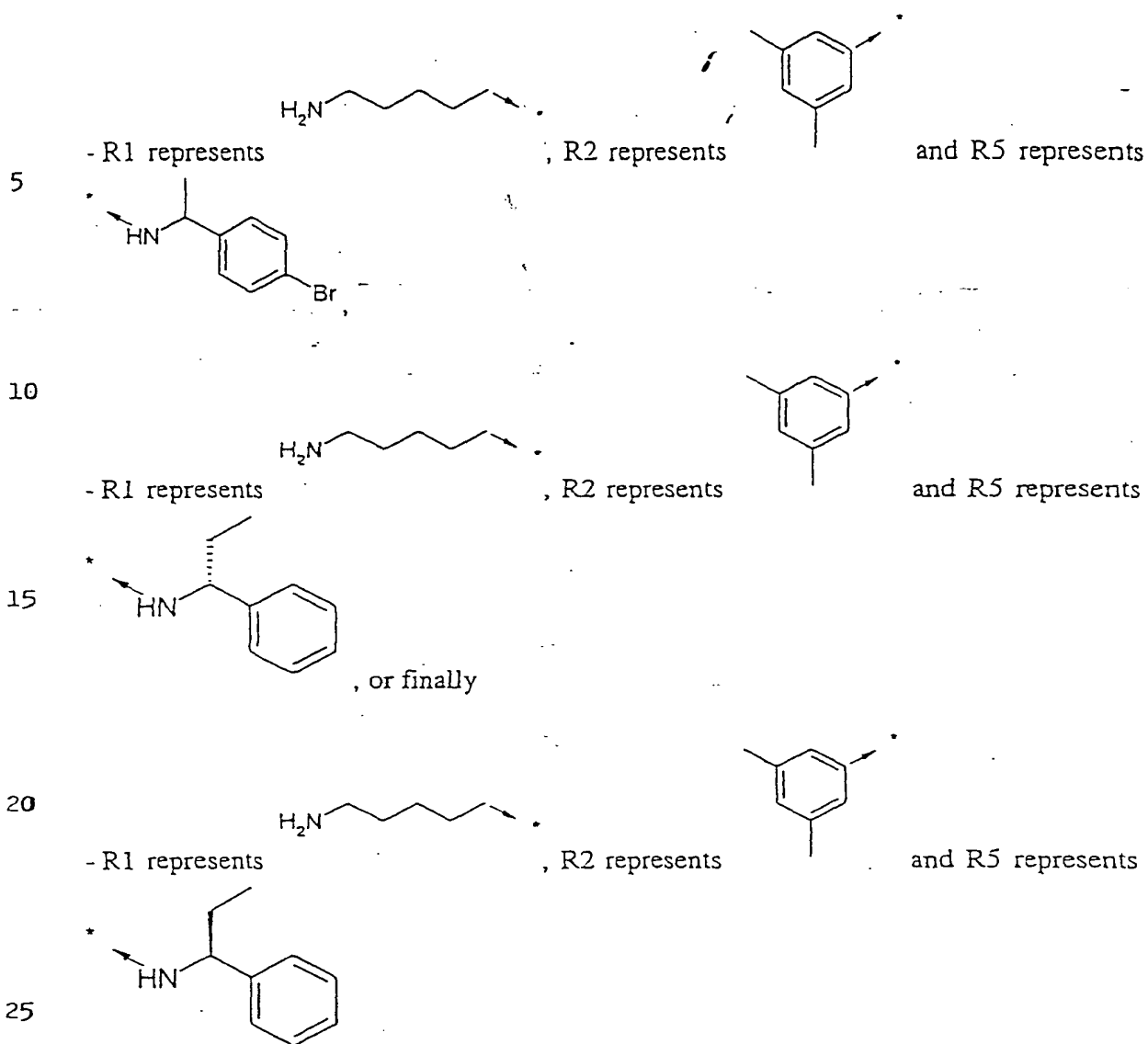
(xv)

in which:







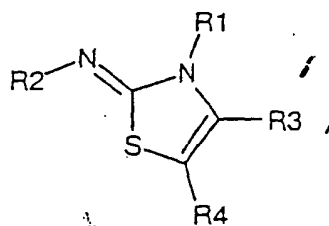


or salt of one of these compounds.

30 In other words, the compounds described in Examples 1642 to 1654, 1656 to 1680, 2468 to 2502, 2525 to 2550, 2556 to 2582, 2605 to 2611, 2614, 2623 to 2630, 2632 to 2646, 2670 to 2678, 2680 to 2694, 2702 to 2710, 2712 to 2726 and 2827 to 2836 or a salt of one of these compounds will be preferred. The compounds of Examples 2827 to 2836 or their salts will be even more particularly preferred.

35 Moreover, the invention relates to preparation processes on a solid support for the compounds of general formula (I) described previously (also applicable to the corresponding compounds of general formula (II)).

According to the invention, the compounds of general formula (I)a



(I)a

in which:

R1 represents a  $-\text{CH}_2\text{-A1-NH}_2$  radical, in which A1 represents a  $-(\text{CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-O-}$ ,  $(\text{CH}_2)_p-$ , aralkylene or cycloalkylalkylene radical, n and p represent integers from 1 to

6;

R2 and R4 represent the same radicals as in general formula (I);

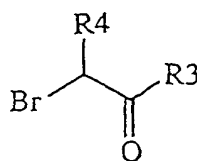
and R3 represents the same radicals as in general formula (I), with the exception of the  $-\text{CO-R5}$  radicals;

can be prepared for example according to a process characterized in that it comprises the following successive stages:

1) treatment, in an aprotic solvent such as dichloromethane or dimethylformamide, of a p-nitrophenylcarbonate Wang resin with a large excess of  $\text{R1-NH}_2$  symmetrical diamine;

2) treatment, in an aprotic solvent such as dichloromethane or dimethylformamide, of the resin isolated after stage 1) with an aromatic isothiocyanate of general formula  $\text{R2-N=C=S}$  in which the R2 radical has the same meaning as in general formula (I)a;

3) treatment, in an aprotic solvent such as dioxane or dimethylformamide, of the resin obtained in Stage 2) with the compound of general formula (III)



(III)

in which the R3 and R4 radicals have the same meaning as in general formula (I)a;

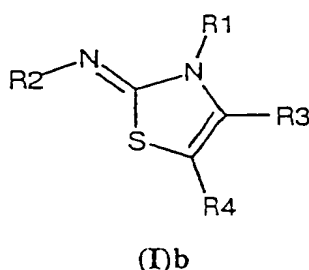
4) cleavage of the resin under acid conditions;

5) treatment under basic conditions of the product obtained after Stage 4).

5 The preparation of the p-nitrophenylcarbonate Wang resin is described further on in the part entitled "PREPARATION OF THE COMPOUNDS OF THE INVENTION".

10 Preferably, for the above process, in order to have the large excess in Stage 1), of the order of 10 to 20 equivalents of diamine R1-NH<sub>2</sub> will be used. Stage 1) is preferably carried out at ambient temperature. Stage 3) is carried out at a temperature greater than ambient temperature, for example at a temperature comprised between 60 and 90 °C, using of the order of 2 to 5 equivalents of the compound of general formula (III). In Stage 4), the acid conditions can for example be created by using a dichloromethane / trifluoroacetic acid mixture at 50 %, said acid conditions being preferably maintained for a duration of the order of 1 to 2 hours. In Stage 5), the basic conditions can for example be created by using a saturated solution of sodium hydrogen carbonate or by  
15 elution on a basic alumina cartridge.

According to a variant of the invention, the compounds of general formula (I)b



in which:

R1 represents the same radicals as in general formula (I), with the exception of the -CH<sub>2</sub>-A1-NH<sub>2</sub> type radicals, in which A1 represents a -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>p</sub>-,  
20 aralkylene or cycloalkylalkylene radical, n and p representing integers from 1 to 6, and also with the exception of the -C(R11)(R12)-CO-R10 radicals;

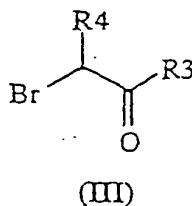
R2 represents an aminoalkylphenyl radical;

R3 represents the same radicals as in general formula (I), with the exception of the -CO-R5 radicals;

25 and R4 represents the same radicals as in general formula (I):

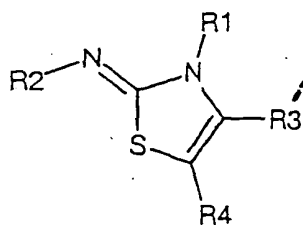
can be prepared for example according to a process characterized in that it comprises the following successive stages:

- 1) treatment, in an aprotic solvent such as dichloromethane or dimethylformamide, of a Wang resin p-nitrophenylcarbonate with an excess of aminoalkylaniline of general formula  $R_2-NH_2$  in which the  $R_2$  radical has the same meaning as in general formula (I)b;  
5
- 2) treatment, in an aprotic solvent such as dichloromethane or dimethylformamide, of the resin isolated after Stage 1) with an isothiocyanate of general formula  $R_1-N=C=S$  in which the  $R_1$  radical has the same meaning as in general formula (I)b;
- 10 3) treatment, in an aprotic solvent such as dioxane or dimethylformamide, of the resin obtained in Stage 2) with the compound of general formula (III)



in which the  $R_3$  and  $R_4$  radicals have the same meaning as in general formula (I)b;

- 4) cleavage of the resin under acid conditions;
  - 5) treatment under basic conditions of the product obtained after Stage 4).
- 15 Preferably, for the above process, in order to have the excess in Stage 1), of the order of 5 to 10 equivalents of aminoalkylaniline will be used. Stage 1) is preferably carried out at ambient temperature. Stage 3) is carried out at a temperature greater than ambient temperature, for example at a temperature comprised between 60 and 90 °C, using of the order of 2 to 5 equivalents of the compound of general formula (III). In Stage 4),  
20 the acid conditions can for example be created by using a dichloromethane / trifluoroacetic acid mixture at 50 %, said acid conditions being preferably maintained for a duration of the order of 1 to 2 hours. In Stage 5), the basic conditions can for example be created by using a saturated solution of sodium hydrogen carbonate or by elution on a basic alumina cartridge.
- 25 According to another variant of the invention, the compounds of general formula (I)c



(I)c

in which:

R1 represents a  $-\text{CH}_2\text{-A1-NH}_2$  radical, in which A1 represents a  $-(\text{CH}_2)_n-$ ,  $-(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_p-$ , aralkylene or cycloalkylalkylene radical, n and p representing integers from 1 to 6;

5 R2 represents the same radicals as in general formula (I);

R3 represents a  $-\text{CO-R5}$  radical;

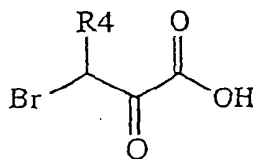
and R4 and R5 represent the same radicals as in general formula (I);

can be prepared according to a process characterized in that it comprises the following successive stages:

10 1) treatment, in an aprotic solvent such as dichloromethane or dimethylformamide, of a Wang resin p-nitrophenylcarbonate with a large excess of symmetrical diamine of general formula  $\text{R1-NH}_2$  in which the R1 radical has the same meaning as in general formula (I)c;

15 2) treatment, in an aprotic solvent such as dichloromethane or dimethylformamide, of the resin isolated after Stage 1) with an aromatic isothiocyanate of general formula  $\text{R2-N=C=S}$  in which the R2 radical has the same meaning as in general formula (I)c;

3) treatment, in an aprotic solvent such as dioxane or dimethylformamide, of the resin obtained in Stage 2) with the acid of general formula (IV)



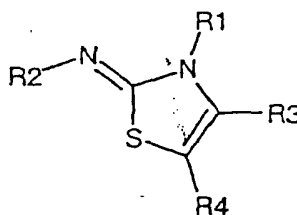
(IV)

in which the R4 radical has the same meaning as in general formula (I)c;

- 4) peptide coupling;
- 5) cleavage of the resin under acid conditions;
- 6) treatment under basic conditions of the product obtained after Stage 5).

Preferably, for the above process, in order to have the large excess in Stage 1) of the order of 10 to 20 equivalents of symmetrical diamine will be used. Stage 1) is preferably carried out at ambient temperature. Stage 3) is carried out at a temperature greater than ambient temperature, for example at a temperature comprised between 60 and 90 °C, using of the order of 2 to 5 equivalents of the acid of general formula (IV). The peptide coupling of Stage 4) is carried out for example in DMF with coupling agents such as for example dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), a DIC/N-hydroxybenzotriazole (HOBt) mixture, benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate (PyBOP), 2-(1H-benzotriazol-1-yl)-1.1,3,3-tetramethyluronium hexafluorophosphate (HBTU) or 2-(1H-benzotriazol-1-yl)-1.1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and aminated compounds. Preferably, the coupling agents are used in proportions of 4 to 5 equivalents, as with the aminated compounds, and the reaction will take place at a temperature of the order of ambient temperature for a duration of the order of 1 to 24 hours. In Stage 5), the acid conditions can for example be created by using a dichloromethane / trifluoroacetic acid mixture at 50 %, said acid conditions being preferably maintained for a duration of the order of 1 to 2 hours. In Stage 6), the basic conditions can for example be created by using a saturated solution of sodium hydrogen carbonate or by elution on a basic alumina cartridge.

According to yet another variant, the compounds of general formula (I)d



(I)d

in which:

- 25 R1 represents the same radicals as in general formula (I), with the exception of the -CH<sub>2</sub>-A1-NH<sub>2</sub> type radicals, in which A1 represents a -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>p</sub>-,

aralkylene or cycloalkylalkylene radical, n and p represent integers from 1 to 6, and also with the exception of the  $-C(R_{11})(R_{12})-CO-R_{10}$  radicals;

R<sub>2</sub> represents an aminoalkylphenyl radical;

R<sub>3</sub> represents a  $-CO-R_5$  radical;

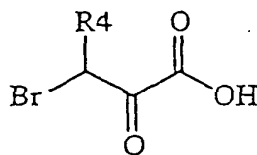
5 and R<sub>4</sub> and R<sub>5</sub> represent the same radicals as in general formula (I);

can be prepared according to a process characterized in that it comprises the following successive stages:

1) treatment, in an aprotic solvent such as dichloromethane or dimethylformamide, of a Wang resin p-nitrophenylcarbonate with an excess of aminoalkylaniline of general  
10 formula  $R_2-NH_2$  in which the R<sub>2</sub> radical has the same meaning as in general formula (I)d;

2) treatment, in an aprotic solvent such as dichloromethane or dimethylformamide, of the resin isolated after Stage 1) with an isothiocyanate of general formula  $R_1-N=C=S$  in which the R<sub>1</sub> radical has the same meaning as in general formula (I)d;

15 3) treatment, in an aprotic solvent such as dioxane or dimethylformamide, of the resin obtained in Stage 2) with the acid of general formula (IV)



(IV)

in which the R<sub>4</sub> radical has the same meaning as in general formula (I)d;

4) peptide coupling;

5) cleavage of the resin under acid conditions;

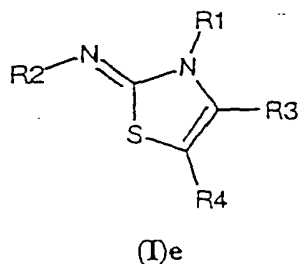
20 6) treatment under basic conditions of the product obtained after Stage 5).

Preferably, for the above process, in order to have the excess in Stage 1), of the order of 5 to 10 equivalents of aminoalkylaniline will be used. Stage 1) is preferably carried out at ambient temperature. Stage 3) is carried out at a temperature greater than ambient temperature, for example at a temperature comprised between 60 and 90 °C, using of



the order of 2 to 5 equivalents of the acid of general formula (IV). The peptide coupling of Stage 4) is carried out for example in DMF with coupling agents such as for example dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), a DIC/N-hydroxybenzotriazole (HOBt) mixture, benzotriazolyloxytris(dimethylamino) phosphonium hexafluorophosphate (PyBOP), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) or 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and aminated compounds. Preferably, the coupling agents are used in proportions of 4 to 5 equivalents, as with the aminated compounds, and the reaction will take place at a temperature of the order of ambient temperature for a duration of the order of 1 to 24 hours. In Stage 5), the acid conditions can for example be created by using a dichloromethane / trifluoroacetic acid mixture at 50 %, said acid conditions being preferably maintained for a duration of the order of 1 to 2 hours. In Stage 6), the basic conditions can for example be created by using a saturated solution of sodium hydrogen carbonate or by elution on a basic alumina cartridge.

According to another variant, the compounds of general formula (I)e



in which:

R1 represents the same radicals as in general formula (I), with the exception of the -CH<sub>2</sub>-A1-NH<sub>2</sub> type radicals, in which A1 represents a -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>p</sub>-, aralkylene or cycloalkylalkylene radical, n and p representing integers from 1 to 6, and also with the exception of the -C(R11)(R12)-CO-R10 radicals;

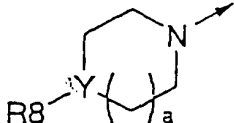
R2 represents the same radicals as in general formula (I);

R3 represents a -CO-R5 radical;

R4 represents H;

R5 represents an -NH-CH<sub>2</sub>-A1-NH<sub>2</sub> radical, in which A1 represents a linear or branched alkylene radical containing 1 to 6 carbon atoms, -(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>p</sub>-,

aralkylene or cycloalkylalkylene, n and p representing integers from 1 to 6, or also R5 represents the N(R6)(R7) radical corresponding to the following general formula:



in which:

R8 represents H;

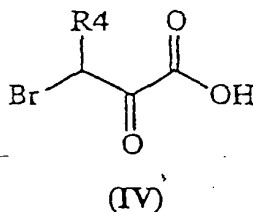
5 Y represents N;

a represents 1 or 2;

can be prepared by a process characterized in that it comprises the following successive stages:

1) treatment, in an aprotic solvent such as dichloromethane or dimethylformamide, of a  
10 Wang resin p-nitrophenylcarbonate with a large excess of symmetrical diamine of general formula R5-H;

2) peptide coupling with the acid of general formula (IV) on the resin obtained in Stage 1)



in which the R4 radical has the same meaning as in general formula (I)e;

15 3) reaction of the primary amine of general formula R1-NH<sub>2</sub> with the isothiocyanate of general formula R2-NCS in a solvent such as dimethylformamide or dioxane, R1 and R2 having the same meanings as in general formula (I)e;

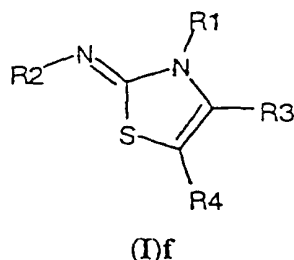
4) addition of the thiourea obtained in Stage 3) to the resin obtained in Stage 2) and heating the mixture;

20 5) cleavage of the resin under acid conditions;

6) treatment under basic conditions of the product obtained after Stage 5).

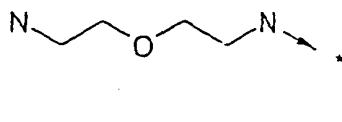
Preferably, for the above process, in order to have the large excess in Stage 1), of the order of 10 to 20 equivalents of diamine R5-H will be used. Stage 1) is preferably carried out at ambient temperature. The peptide coupling of Stage 2) is carried out in DMF with a coupling agent such as for example the DIC/N-hydroxybenzotriazole (HOBt) mixture. Preferably, the reaction of Stage 3) is carried out in a solvent such as dimethylformamide or dioxane. During the addition of Stage 4), 2 to 5 equivalents of thiourea will preferably be used per equivalent of resin; preferably also, heating will be carried out at a temperature greater than ambient temperature, for example at a temperature from 40 to 100°C (in particular at a temperature of approximately 80°C) and for a duration of 2 to 24 hours. In Stage 5), the acid conditions can for example be created by using a dichloromethane / trifluoroacetic acid mixture at 50 %, said acid conditions being preferably maintained for a duration of the order of 1 to 2 hours. In Stage 6), the basic conditions can for example be created by using a saturated solution of sodium hydrogen carbonate or by elution on a basic alumina cartridge.

According to yet another variant, the compounds of general formula (If)



in which:

- R1 represents a  $-C(R11)(R12)-CO-R10$  radical;
- R2, R3 and R4 represent the same radicals as in general formula (I);
- R10 represents an amino(C<sub>2</sub>-C<sub>7</sub>)alkylamino, ((aminoalkyl)aryl)alkylamino, ((aminoalkyl)cycloalkyl)alkylamino, piperaziny, homopiperaziny radical,
- or R10 represents the radical represented below:



R11 represents H;

R12 represents H or an alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, optionally substituted carbocyclic or heterocyclic aralkyl, propargyl, allyl, hydroxyalkyl, alkylthioalkyl, arylalkylalkoxyalkyl, arylalkylthioalkoxyalkyl radical;

5 can be prepared by a process characterized in that it comprises the following successive stages:

- 1) treatment, in an aprotic solvent such as dichloromethane or dimethylformamide, of a Wang resin p-nitrophenylcarbonate with a large excess of symmetrical diamine of general formula R10-H in which R10 has the same meaning as in general formula (I)f;
- 10 2) peptide coupling of the resin obtained in Stage 1) with an amino acid of general formula HOOC-C(R11)(R12)-NH-Fmoc in which R11 and R12 have the same meaning as in general formula (I)f;
- 3) cleavage of the Fmoc group from the resin obtained in Stage 2);
- 4) reaction of the resin obtained in Stage 3) with an isothiocyanate of general formula  
15 R2-NCS in which R2 has the same meaning as in general formula (I)f;
- 5) cleavage of the resin under acid conditions;
- 6) treatment under basic conditions of the product obtained after Stage 5).

Preferably, for the above process, in order to have the large excess in Stage 1), of the order of 10 to 20 equivalents of diamine R10-H will be used. Stage 1) is preferably  
20 carried out at ambient temperature. The peptide coupling of Stage 2) is carried out for example in DMF with coupling agents such as for example dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), a DIC/N-hydroxybenzotriazole (HOBt) mixture, benzotriazolyloxytris(dimethylamino) phosphonium hexafluorophosphate (PyBOP), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate  
25 (HBTU) or 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU). Preferably, the reaction of Stage 2) is carried out at ambient temperature and for a duration of 1 to 24 hours. The deprotection of Stage 3) can be carried out, for example, by a mixture of DMF containing 20% piperidine. Stage 4) will preferably be carried out in a solvent such as dimethylformamide or dichloromethane, the  
30 isothiocyanate preferably being added in a proportion of 5 to 10 equivalents per equivalent of the resin obtained in Stage 3). In Stage 5), the acid conditions can for example be created by using a dichloromethane / trifluoroacetic acid mixture at 50 %

said acid conditions being preferably maintained for a duration of the order of 1 to 2 hours. In Stage 6), the basic conditions can for example be created by using a saturated solution of sodium hydrogen carbonate or by elution of a basic alumina cartridge.

5 A subject of the invention is also, as medicaments, the compounds of general formulae (I) and (II) described previously or their pharmaceutically acceptable salts. It also relates to pharmaceutical compositions containing said compounds or their pharmaceutically acceptable salts, and their use for the preparation of a medicament intended to treat pathological states or diseases in which one (or more) of the somatostatin receptors are involved.

10 In particular, the compounds of general formulae (I) and (II) described previously or their pharmaceutically acceptable salts can be used for the preparation of a medicament intended to treat pathological states or diseases chosen from the group comprising the following pathological states or diseases: acromegalia, hypophyseal adenomas, Cushing's disease, gonadotrophinomas and prolactinomas, catabolic side-effects of  
15 glucocorticoids, insulin dependent diabetes, diabetic retinopathy, diabetic nephropathy, syndrome X, dawn phenomenon, angiopathy, angioplasty, hyperthyroidism, gigantism, endocrinic gastroenteropancreatic tumours including carcinoid syndrome, VIPoma, insulinoma, nesidioblastoma, hyperinsulinemia, glucagonoma, gastrinoma and Zollinger-Ellison's syndrome, GRFoma as well as acute bleeding of the esophageal  
20 veins, ulcers, gastroesophageal reflux, gastroduodenal reflux, pancreatitis, enterocutaneous and pancreatic fistulae but also diarrhoea, refractory diarrhoea's of acquired immunodeficiency syndrome, chronic secretory diarrhoea, diarrhoea associated with irritable bowel syndrome, diarrhoea's induced by chemotherapy, disorders linked with gastrin releasing peptide, secondary pathologies with intestinal grafts, portal  
25 hypertension as well as haemorrhages of the veins in patients with cirrhosis, gastro-intestinal haemorrhage, haemorrhage of the gastroduodenal ulcer, bleeding of grafted vessels, Crohn's disease, systemic scleroses, dumping syndrome, small intestine syndrome, hypotension, scleroderma and medullar thyroid carcinoma, illnesses linked with cell hyperproliferation such as cancers and more particularly breast cancer,  
30 prostate cancer, thyroid cancer as well as pancreatic cancer and colorectal cancer, fibroses and more particularly fibrosis of the kidney, fibrosis of the liver, fibrosis of the lung, fibrosis of the skin, also fibrosis of the central nervous system as well as that of the nose and fibrosis induced by chemotherapy, and in other therapeutic fields such as, for example, cephalaeas including cephalaea associated with hypophyseal tumours, pain,  
35 inflammatory disorders such as arthritis, panic attacks, chemotherapy, cicatrization of wounds, renal insufficiency resulting from delayed development, hyperlipidemia, obesity and delayed development linked with obesity, delayed uterine development,

dysplasia of the skeleton, Noonan's syndrome, sleep apnea syndrome, Graves' disease, polycystic disease of the ovaries, pancreatic pseudocysts and ascites, leukemia, meningioma, cancerous cachexia, inhibition of H pylori, psoriasis, chronic rejection of allografts as well as Alzheimer's disease and finally osteoporosis.

5 Preferably, the compounds of general formulae (I) and (II) described previously or their pharmaceutically acceptable salts can be used for the preparation of a medicament intended to treat the pathological states or diseases chosen from the group comprising the following pathological states or diseases: acromegalia, hypophyseal adenomas or endocrinic gastroenteropancreatic tumors including carcinoid syndrome, and  
10 gastrointestinal bleeding.

By pharmaceutically acceptable salt is meant in particular addition salts of inorganic acids such as hydrochloride, sulphate, phosphate, diphosphate, hydrobromide and nitrate, or of organic acids, such as acetate, maleate, fumarate, tartrate, succinate, citrate, lactate, methanesulphonate, p-toluenesulphonate, pamoate, oxalate and stearate. The  
15 salts formed from bases such as sodium or potassium hydroxide also fall within the scope of the present invention, when they can be used. For other examples of pharmaceutically acceptable salts, reference can be made to "Pharmaceutical salts", *J. Pharm. Sci.* 66:1 (1977).

The pharmaceutical composition can be in the form of a solid, for example powders,  
20 granules, tablets, capsules, liposomes or suppositories. Appropriate solid supports can be for example calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone and wax. The suspensions contain in particular suspensions of sustained release microparticles loaded with active ingredient (in particular  
25 microparticles of polylactide-co-glycolide or PLGA - cf. for example the Patents US 3,773,919, EP 52 510 or EP 58 481 or the Patent Application PCT WO 98/47489), which allow the administration of a determined daily dose over a period of several days to several weeks.

The pharmaceutical compositions containing a compound of the invention can also be  
30 presented in the form of a liquid, for example, solutions, emulsions, suspensions or syrups. Appropriate liquid supports can be, for example, water, organic solvents such as glycerol or glycols, as well as their mixtures, in varying proportions, in water.

The administration of a medicament according to the invention can be carried out by topical, oral, parenteral route, by intramuscular injection, etc.

The administration dose envisaged for a medicament according to the invention is comprised between 0.1 mg and 10 g according to the type of active compound used.

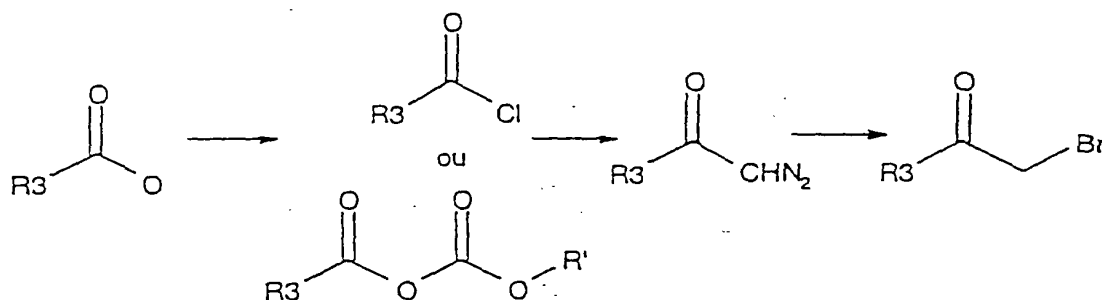
These compounds can be prepared according to the methods described below.

## PREPARATION OF THE COMPOUNDS OF THE INVENTION

### I) Preparation of $\alpha$ -bromoketones

#### FIRST METHOD

This method is inspired by the protocols described in the following publications:  
Macholan, L.; Skursky, L. *Chem. Listy* 1955, 49, 1385-1388; Bestman, H.J.; Seng, F.  
*Chem. Ber.* 1963, 96, 465-469; Jones, R.G.; Kornfeld, E.C.; McLaughlin, K.C. *J. Am.*  
5 *Chem. Soc.* 1950, 72, 4526-4529; Nimgirawath, S.; Ritchie, E.; Taylor, W.C. *Aust. J.*  
*Chem.* 1973, 26, 183-193).



A carboxylic acid is firstly converted to an acid by using oxalyl or thionyl chloride, or by activating it in the form of an anhydride using an alkyl chloroformate (for example isobutyl chloroformate, cf. Krantz, A.; Copp, L.J. *Biochemistry* 1991, 30, 4678-4687; or ethyl chloroformate, cf. Podlech, J.; Seebach, D. *Liebigs Ann.* 1995, 1217-1228) in the  
10 presence of a base (triethylamine or N-methylmorpholine).

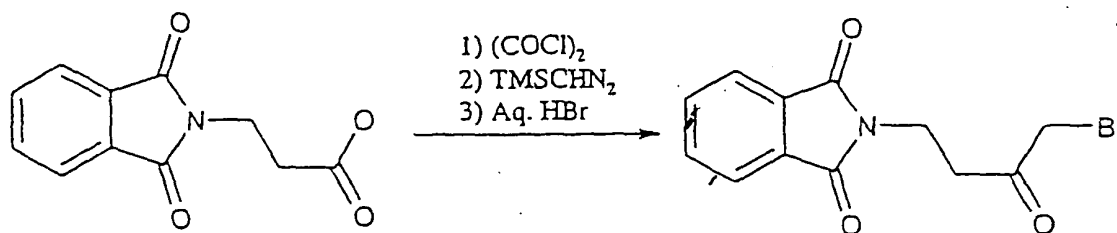
The activated carboxyl group is then converted to diazoketone using diazomethane in an ethereal solution or a commercial solution of trimethylsilyldiazomethane (Aoyama, T.; Shiori, T. *Chem. Pharm. Bull.* 1981, 29, 3249-3255) in an aprotic solvent such as  
15 diethyl ether, tetrahydrofuran (THF) or acetonitrile.

The bromination is then carried out using a bromination agent such as hydrobromic acid in acetic acid, aqueous hydrobromic acid in diethyl ether or dichloromethane.

#### Preparation 1

2-(4-bromo-3-oxobutyl)-1H-isoindole-1,3(2H)-dione  
20 ( $C_{12}H_{10}BrNO_3$ , MM = 296.12):



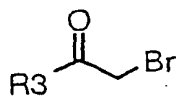


Oxalyl chloride (5.8 ml; 66.7 mmol) is added to Pht- $\beta$ -Ala-OH (9.96g; 44.5 mmol) dissolved in dichloromethane (120ml) and 3 drops of dimethylformamide (DMF). The mixture is agitated for 3 hours at ambient temperature. After elimination of the solvent, the white solid is taken up in a 1:1 mixture of anhydrous tetrahydrofuran and acetonitrile (200 ml) then 49 ml of a 2M solution of (trimethylsilyl) diazomethane in hexane (97.9 mmol) is added dropwise at 0 °C. The solvents are eliminated after agitation overnight at 0 °C. The pale yellow solid is then dissolved in dichloromethane (60 ml) and 12 ml of aqueous hydrobromic acid (48%) is added dropwise at 0 °C. The mixture is agitated until the temperature reaches 15 °C and 50 ml of a saturated solution of sodium bicarbonate is added. The organic phase is washed with salt water then dried over sodium sulphate. Crystallization from diethyl ether allows a white solid to be obtained (11.39 g; yield = 86%).

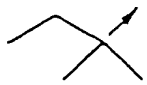
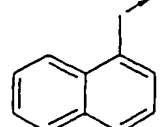
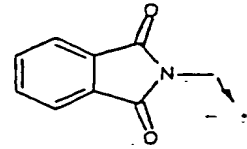
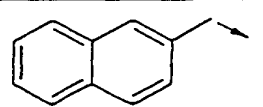
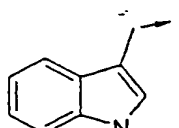
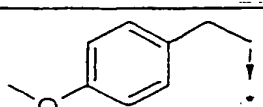
NMR  $^1\text{H}$  (DMSO  $\text{D}_6$ , 100 MHz,  $\delta$ ): 7.83 (s, 4H); 4.36 (s, 2H,  $\text{CH}_2\text{Br}$ ); 3.8 (t, 2H,  $J = 7.1$  Hz,  $\text{NCH}_2$ ); 2.98 (t, 2H,  $J = 6.9$  Hz,  $\text{CH}_2\text{CO}$ ).

### Preparations 2-11

The following compounds were prepared in a similar fashion to the procedure described in Preparation 1:



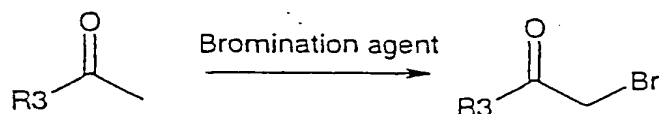
Prep.	R3	Yield (%)	Prep.	R3	Yield (%)
2*		78	7		67
3*		60	8		51

4*		10	9		38
5*		69	10		22
6*		41	11		67

\* Compounds already described in the literature.

## SECOND METHOD

The starting product is an arylmethylketone or a heteroarylmethylketone.

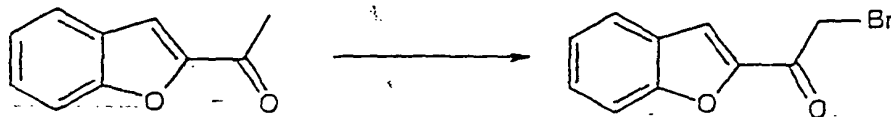


The starting arylmethylketone or heteroarylmethylketone is converted to the corresponding  $\alpha$ -bromoketone by using different brominating agents:

- 5 -  $\text{CuBr}_2$  (King, L.C.; Ostrum, G.K. *J. Org. Chem.* 1964, 29, 3459-3461) heated in ethyl acetate or dioxane;
- N-bromosuccinimide in  $\text{CCl}_4$  or aqueous acetonitrile (Morton, H.E.; Leanna, M.R. *Tetrahedron Lett.* 1993, 34, 4481-4484);
- bromine in glacial acetic acid or sulphuric acid;
- 10 - phenyltrimethylammonium tribromide (Sanchez, J. P.; Parcell, R. P. *J. Heterocyclic Chem.* 1988, 25, 469-474) at 20-80 °C in an aprotic solvent such as THF or tetrabutylammonium tribromide (Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Fujisaki, S. *Bull. Chem. Soc. Jpn.* 1987, 60, 1159-1160) in a dichloromethane/methanol mixture at ambient temperature;
- 15 - brominating agent on a polymer support such as perbromide on an Amberlyst A-26 resin, poly(perbromide of vinylpyridinium hydrobromide) (Frechet, J. M. J.; Farrall, M. J. *J. Macromol. Sci. Chem.* 1977, 507-514) in a protic solvent such as methanol at approximately 20-35 °C for approximately 2-10 hours.

Preparation 12

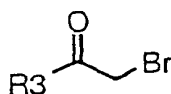
*1-(1-benzofuran-2-yl)-2-bromo-1-ethanone*  
(C<sub>10</sub>H<sub>7</sub>BrO<sub>2</sub>, MM = 239.06):



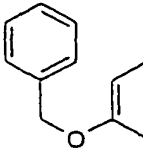
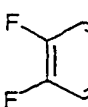
- A polymer of perbromide of pyridine hydrobromide (8.75 g; 17.5 mmol; 1.4 equivalent) is added to a solution of (benzofuran-2-yl)methylketone (2 g; 12.5 mmol) in methanol (40 ml). The resulting mixture is agitated at ambient temperature for 7 hours and the reaction is stopped by filtration. The methanol is eliminated under reduced pressure and an additional addition of diethyl ether allows crystallization of the expected product (3.6 g; yield = 60%).
- NMR <sup>1</sup>H (DMSO D6, 100 MHz, δ): 8.09 (s, 1H); 7.98 (d, 1H, J = 6.6 Hz); 7.75 (d, 1H, J = 8.4 Hz); 7.58 (t, 1H, J = 8.4 Hz); 7.4 (t, 1H, J = 7 Hz); 4.83 (s, 2H, CH<sub>2</sub>Br).

Preparations 8-12

The following compounds were prepared in a similar fashion to the procedure described in Preparation 12:



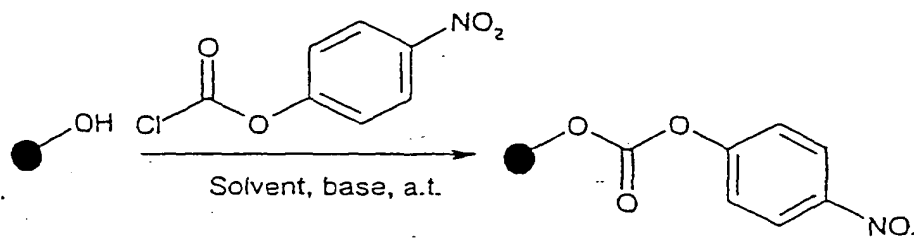
Prep.	R3	Duration of reaction (hrs)	Yield (%)
13*		8	78
14*		2	62
15*		10	56
16*		2	53

17*		3	95
18		8	27

\* Compound already described in the literature.

## II) Synthesis of 2-arylimino-2,3-dihydrothiazoles via synthesis on solid phase

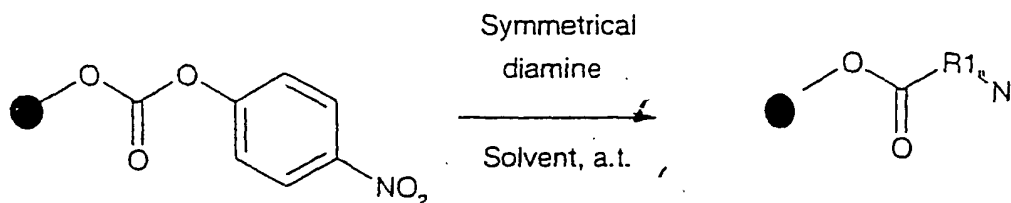
### Preparation of Wang resin p-nitrophenylcarbonate



This resin was prepared from Wang resin, acquired from Bachem or Novabiochem with a load greater than 0.89 mmol/g, by a well described general procedure (cf. Bunin, B.A. *The Combinatorial Index*, Academic Press, 1998, p. 62-63; Dressman, B.A.; Spangle, L.A.; Kaldor, S.W. *Tetrahedron Lett.* 1996, 37, 937-940; Hauske, J.R.; Dorff, P. *Tetrahedron Lett.* 1995, 36, 1589-1592; Cao, J.; Cuny, G.D.; Hauske, J.R. *Molecular Diversity* 1998, 3, 173-179): N-methylmorpholine or pyridine as base and 4-nitrophenylchloroformate are successively added to a Wang resin pre-swollen in dichloromethane (DCM) or tetrahydrofuran (THF) at ambient temperature. The mixture is agitated overnight. The resin is then washed successively with THF, diethyl ether and DCM then dried overnight under reduced pressure at 50 °C.

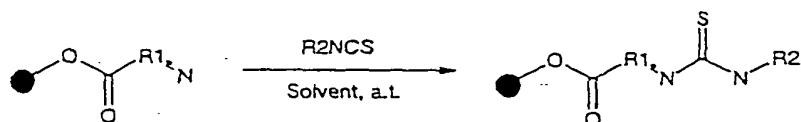
### METHOD A

#### Preparation of monoprotected symmetrical diamines



- General procedure: as already described in the literature (Dixit, D.M.; Leznoff, C.C. *J. C. S. Chem. Comm.* 1977, 798-799; Dixit, D.M.; Leznoff, C.C. *Israel J. Chem.* 1978, 17, 248-252; Kaljuste K.; Unden, A. *Tetrahedron Lett.* 1995, 36, 9211-9214; Munson, M.C.; Cook, A.W.; Josey, J.A.; Rao, C. *Tetrahedron Lett.* 1998, 39, 7223-7226), a Wang resin p-nitrophenylcarbonate is treated with a large excess of symmetrical diamine (10-20 equivalents), in an aprotic solvent such as DCM or DMF, in order to produce a monoprotected diamine resin after agitation overnight.

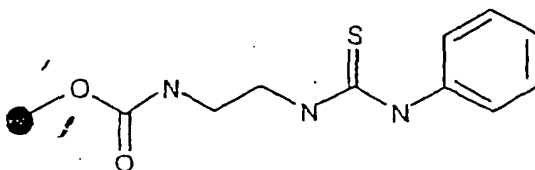
#### Preparation of thiourea resins



- General procedure: aromatic and heteroaromatic isothiocyanates (5-10 equivalents) are added (Smith, J.; Liras, J.L.; Schneider, S.E.; Anslyn, E.V. *J. Org. Chem.* 1996, 61, 8811-8818) to monoprotected symmetrical diamines in a solvent such as DCM or DMF agitated overnight at ambient temperature. Washed successively with DMF and DCM, the thiourea resin is isolated then dried overnight under reduced pressure at 50 °C.

#### Preparation 19

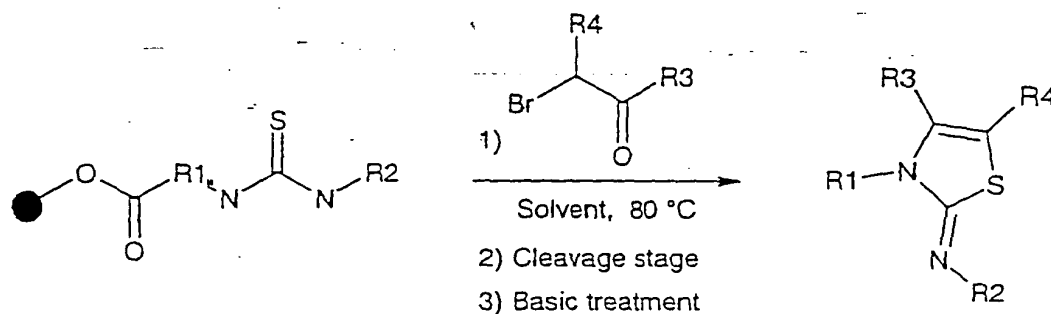
- (phenylaminothioyl)ethyl Wang resin carbamate



Phenylisothiocyanate (1 ml; 8.5 mmol; 5 eq.) is added to an ethylene diamine Wang resin N-carbamate (2 g; 1.72 mmol; 0.86 mmol/g) swollen in DCM (50 ml). After agitation overnight at ambient temperature, the resin is washed successively with DMF (5 x 20 ml) and DCM (5 x 20 ml). The success of the coupling is monitored using the

Kaiser ninhydrin test (Kaiser, E.; Colescott, R.L.; Bossinger, C.D.; Cook, P.I. *Anal Biochem.* 1970, 34, 595-598). A pale yellow resin (1.79 g) is obtained with a load of 0.648 mmol/g calculated from the elemental analysis of sulphur.

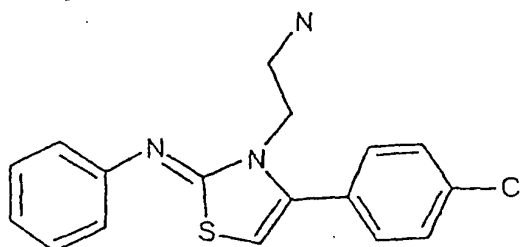
### Synthesis of 2-arylimino-2,3-dihydrothiazoles



- 5 General procedure: regioselective cyclization stage (Korohoda, M.J.; Bojarska, A.B. *Polish J. Chem.* 1984, 58, 447-453; Ragab, F.A.; Hussein, M.M.; Hanna, M.M.; Hassan, G.S.; Kenawy, S.A. *Egypt. J. Pharm. Sci.* 1993, 34, 387-400; Hassan, H.Y.; El-Koussi, N.A.; Farghaly, Z.S. *Chem. Pharm. Bull.* 1998, 46, 863-866) takes place in aprotic solvents such as dioxane or DMF at 80 °C for 2-3 hours between the thiourea resin and the  $\alpha$ -bromoketone (2-5 equivalents). The resin is then washed successively with DMF, methanol and DCM then dried under reduced pressure. The 2-arylimino-2,3-dihydrothiazole resin is cleaved under acid conditions (DCM/trifluoroacetic acid at 50%) for 1-2 hours then rinsed with DCM. The solvent is evaporated off and the free base is isolated after treatment under basic conditions (saturated solution of sodium hydrogen carbonate), extraction with DCM or elution with methanol in a basic alumina cartridge (500 mg, Interchim).

### Example 1

*N*-[3-(2-aminoethyl)-4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]aniline  
(C<sub>17</sub>H<sub>16</sub>ClN<sub>3</sub>S, MM = 329.86):



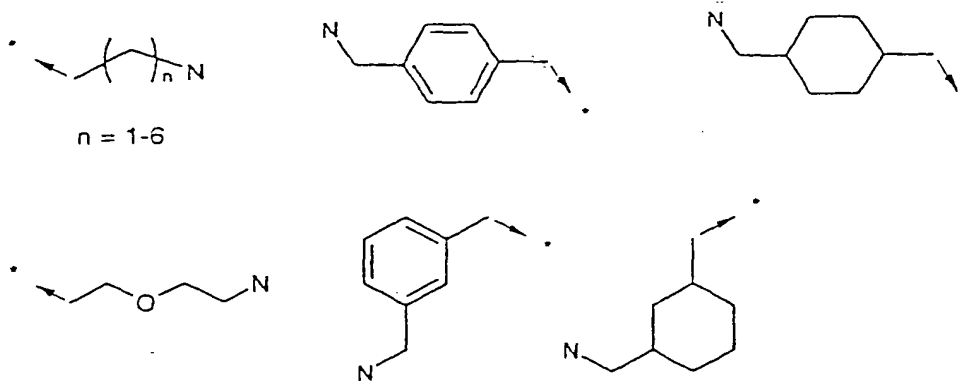
2-bromo-4'-chloroacetophenone (30.2 mg; 129  $\mu$ mol; 2 eq.) dissolved in DMF (1 ml) is added to a thiourea resin prepared above (100 mg; 64.8  $\mu$ mol; load of 0.648 mmol/g). The mixture is agitated for 2 hours at 80 °C. The resin is then successively washed with DMF (3 x 2 ml), methanol (3 x 2 ml) and DCM (3 x 2 ml). The release stage, carried out in 1 ml of a mixture of DCM/trifluoroacetic acid at 50%, produces an oil after one hour 30 minutes of agitation which is eluted with methanol in a basic alumina cartridge (500 mg, Interchim). The free base is isolated in a quantitative fashion (21.3 mg) in the form of a yellow oil having a purity measured by UV spectrophotometry of 98% at 220 nm.

10 NMR  $^1\text{H}$  (DMSO  $\text{D}_6$ , 100 MHz)  $\delta$ : 7.55 (s, 5H); 7.3 (d, 2H,  $J = 7.1$  Hz); 6.99 (d, 2H,  $J = 7.1$  Hz); 6.21 (s, 1H, H azole); 3.74 (t, 2H,  $J = 6.2$  Hz,  $\text{NCH}_2$ ); 3.32 (broad s, 2H,  $\text{NH}_2$ ); 2.72 (t, 2H,  $J = 6.2$  Hz,  $\text{NCH}_2$ ). SM/LC:  $m/z = 330$  ( $\text{M} + \text{H}$ ) $^+$ .

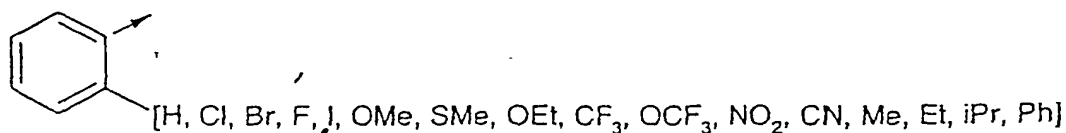
A series of 2-arylimino-2,3-dihydrothiazoles was synthesized according to method A using our robotic system (ACT MOS 496):

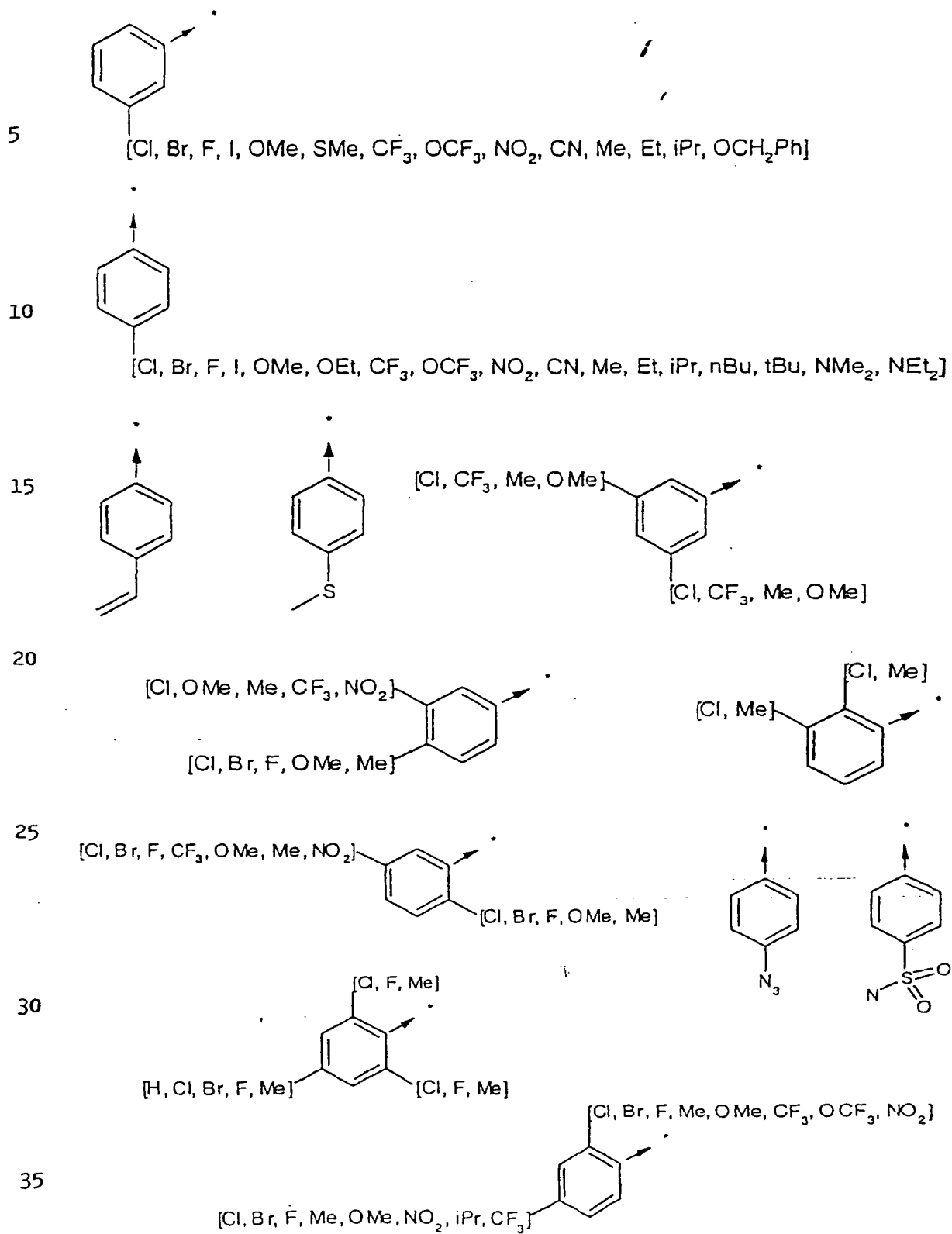
15

R1 groups:

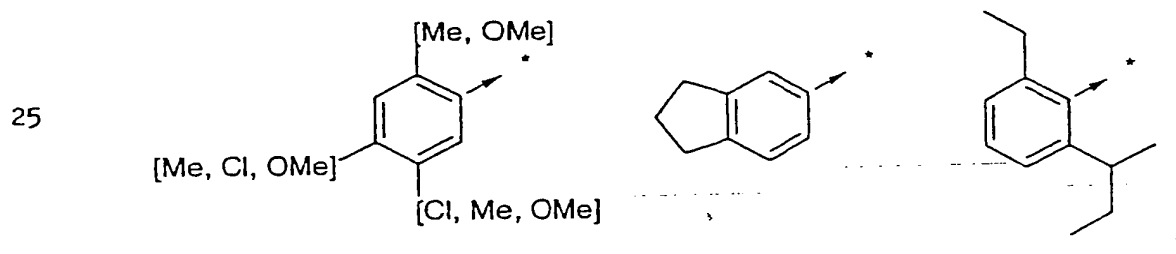
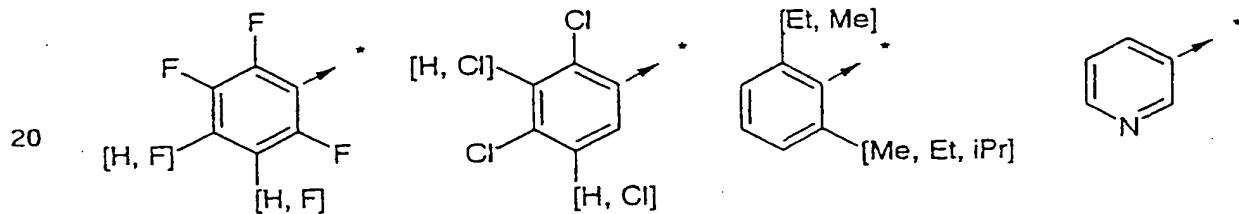
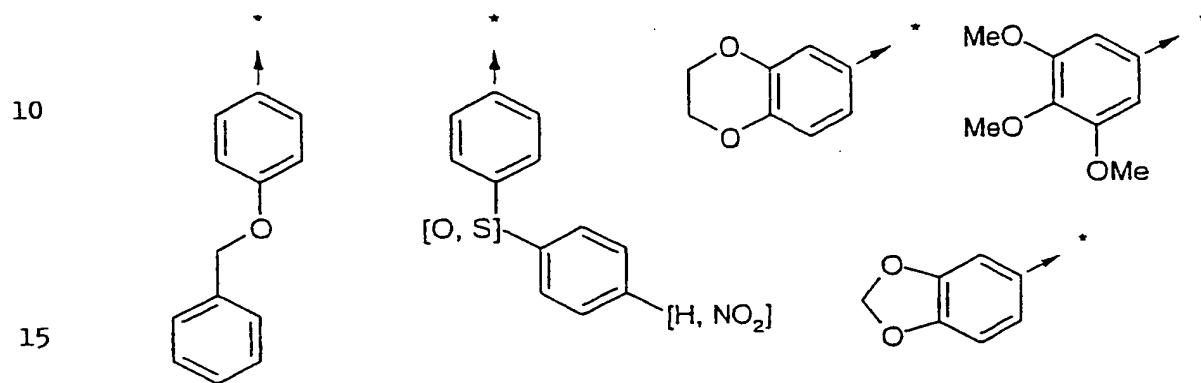
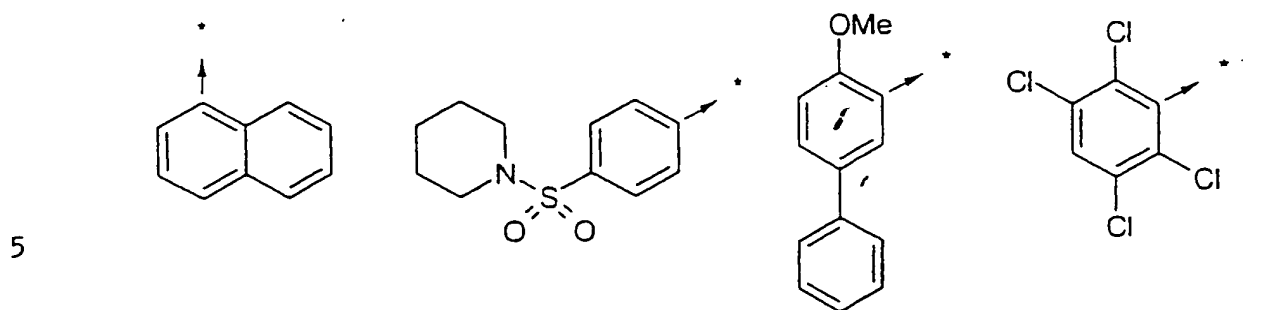


R2 groups:

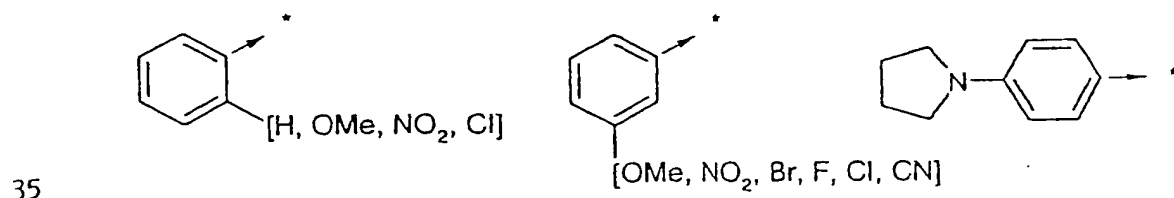


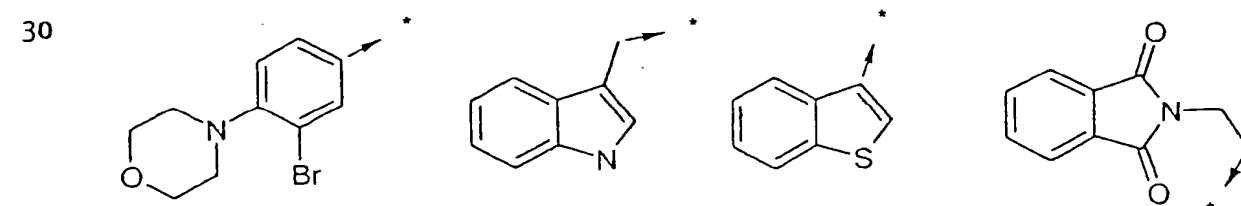
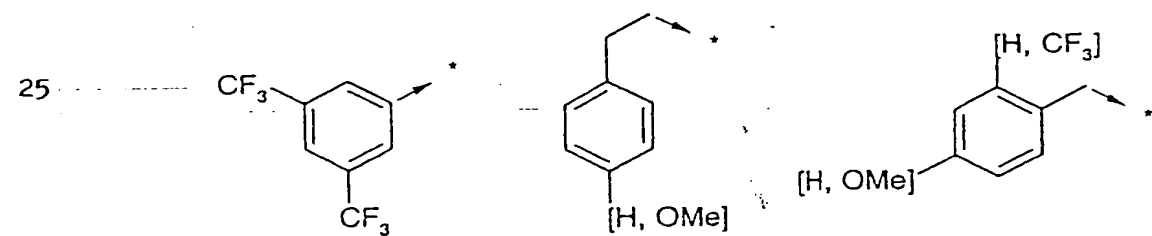
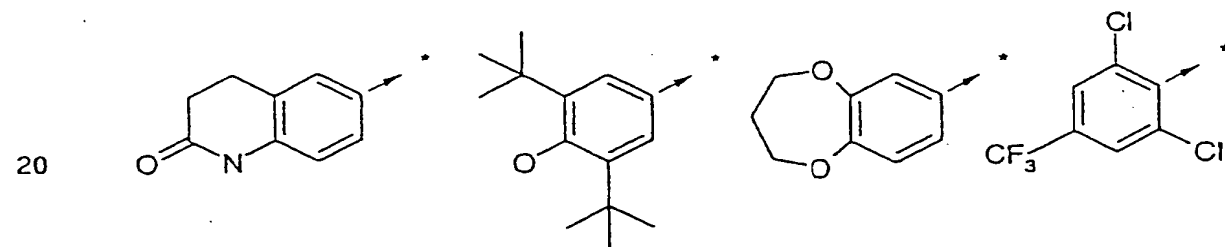
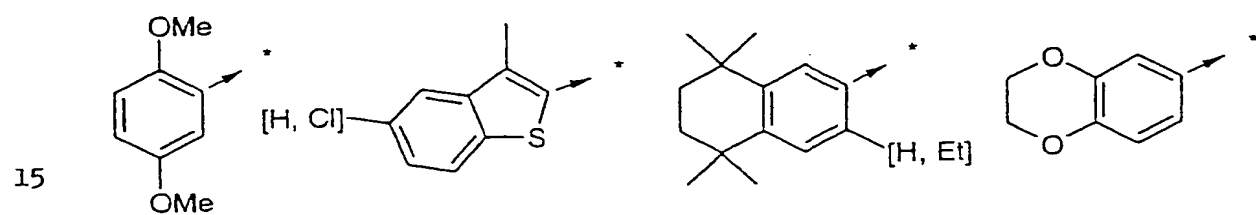
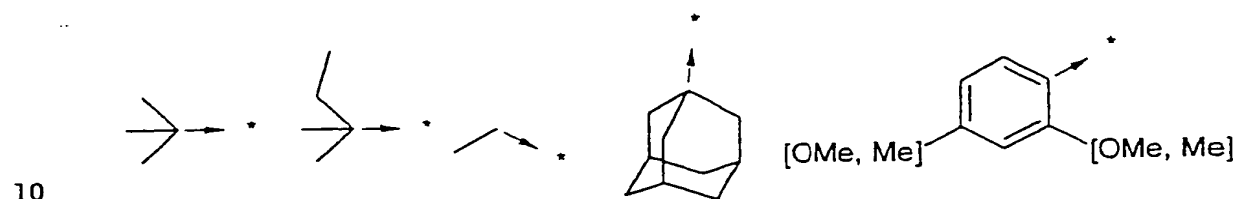
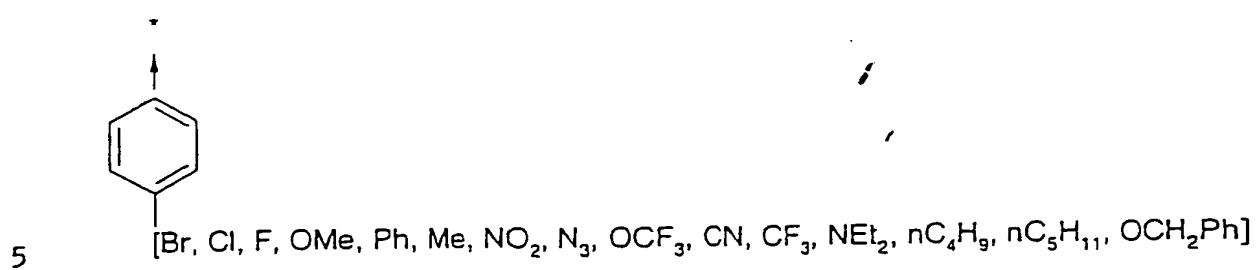


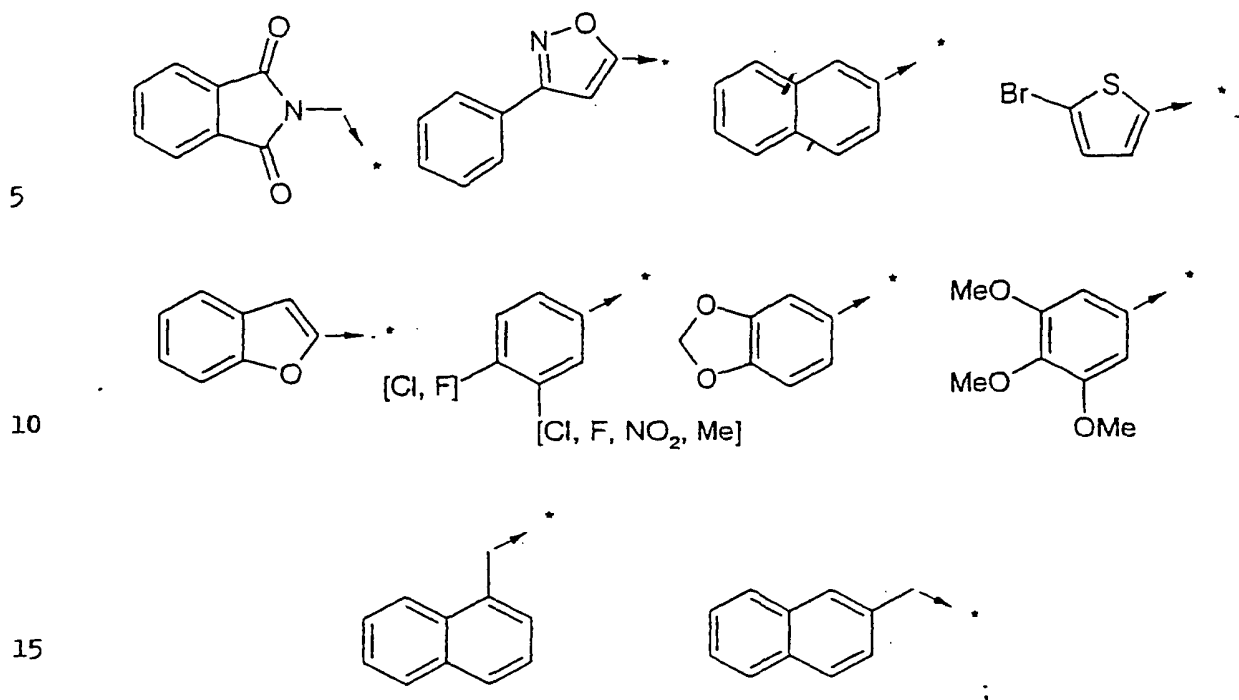




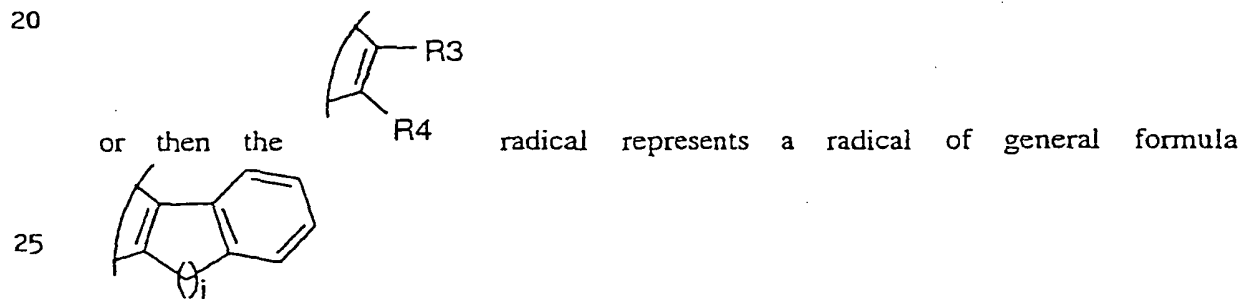
30 R3 groups:







R4 represents H, alkyl, carbocyclic or heterocyclic aralkyl optionally situated on the aryl radical;

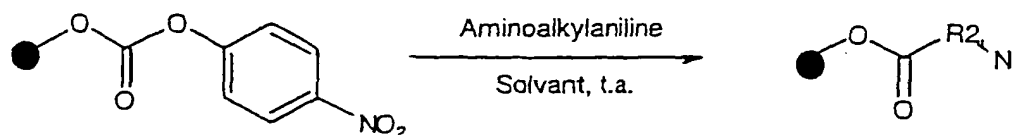


in which i represents an integer from 1 to 3;

30 it being understood that for R4, when the aryl group is substituted, it can be 1 to 5 times (other than the bond which links it to the remainder of the molecule) by radicals chosen independently from the group composed of a halogen atom and an alkyl or alkoxy radical.

## METHOD B

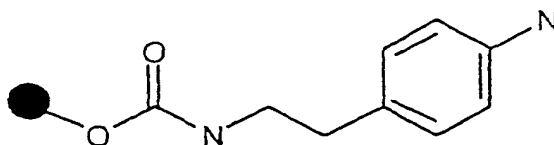
### Preparation of Wang resin carbamates from aminoalkylanilines



General procedure: as already described (Hulme, C.; Peng, J.; Morton, G.; Salvino, J.M.; Herpin, T.; Labaudiniere, R. *Tetrahedron Lett.* 1998, 39, 7227-7230), a p-nitrophenylcarbonate Wang resin is treated with an excess of aminoalkylaniline (5-10 eq.) in DCM or DMF and agitated at ambient temperature overnight. The resin is washed successively with DMF, methanol and DCM then dried overnight under reduced pressure at 50 °C.

### Preparation 20

#### 4-aminophenylethyl Wang resin carbamate

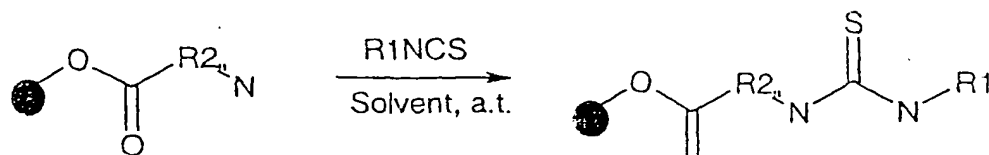


10

A solution of 2-(4-aminophenyl)ethylamine (2.48 g; 17.3 mmol; 5 eq.) in 30 ml of anhydrous DMF is added to a Wang resin p-nitrophenylcarbonate (4.05 g; 3.47 mmol; load of 0.857 mmol/g) pre-swollen in 50 ml of anhydrous DMF. The mixture is agitated at ambient temperature overnight and filtered. The resin is washed successively with DMF (10 x 30 ml), methanol (5 x 30 ml) and DCM (5 x 30 ml). 3.7 g of yellow resin (load of 0.8 mmol/g calculated from the elemental analysis of the nitrogen), giving a positive Kaiser ninhydrin test, is isolated after drying overnight under reduced pressure at 50 °C.

15

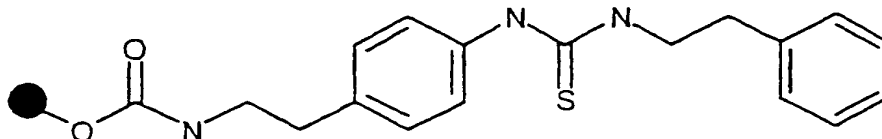
### Preparation of thiourea resins with aliphatic isothiocyanates



General procedure: aliphatic isothiocyanates (5-10 equivalents) are added to an aminoalkylaniline resin in a solvent such as DCM or DMF and agitation is carried out overnight at ambient temperature. After washing successively with DMF and DCM, the thiourea resin is isolated and dried overnight under reduced pressure at 50 °C.

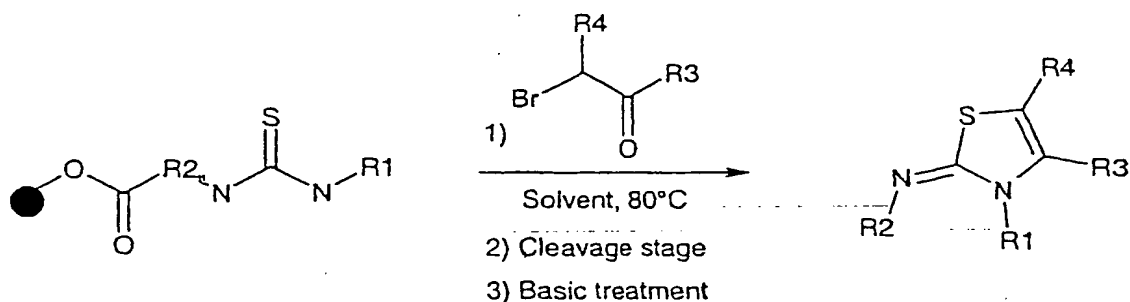
### Preparation 21

4-[[[(phenylethylamino)carbothioyl]amino]-phenylethyl Wang resin carbamate



10 ml of anhydrous DMF and phenylethylisothiocyanate (624  $\mu$ l, 4 mmol, 10 eq.) are added under an argon atmosphere to the resin described previously (0.5 g; 0.4 mmol; load of 0.8 mmol/g). The reaction medium is agitated overnight at ambient temperature and produces a negative Kaiser ninhydrin test. The resin is then washed successively with DMF (5 x 20 ml) and DCM (5 x 20 ml). Drying under reduced pressure at 50 °C produces 488 mg of resin with a load of 0.629 mmol/g calculated from elemental analysis of the sulphur.

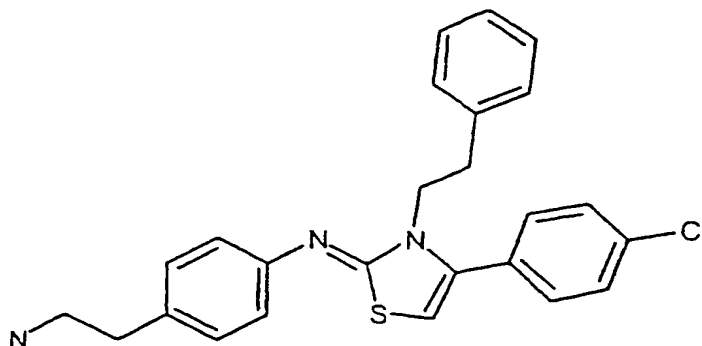
### 15 Synthesis of 2-arylimino-2,3-dihydrothiazoles



General procedure: the cyclization stage takes place in aprotic solvents such as dioxane or DMF at 80 °C for 2 hours between the thiourea resin and the  $\alpha$ -bromoketone (2-5 equivalents). The resin is then washed successively with DMF, methanol and DCM then dried under reduced pressure. The iminothiazole resin is cleaved by treatment under acid conditions (DCM/trifluoroacetic acid at 50%) for 1-2 hours then rinsed with DCM. The solvent is evaporated off and the free base isolated after extraction under basic conditions (saturated solution of sodium hydrogen carbonate), extraction with DCM or elution with methanol in a basic alumina cartridge (500 mg, Interchim).

### Example 2

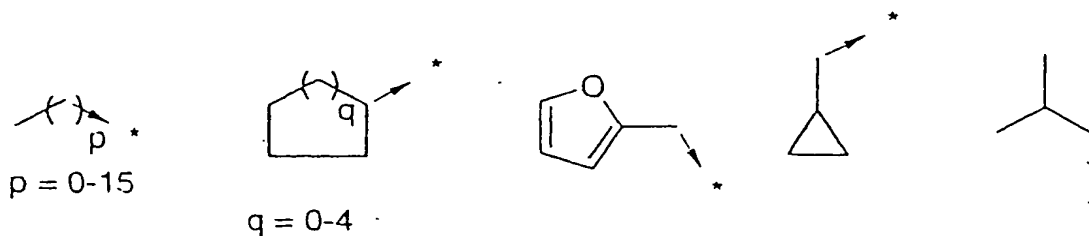
*4-(2-aminoethyl)-N-[4-(4-chlorophenyl)-3-phenethyl-1,3-thiazol-2(3H)-ylidene]aniline*  
(C<sub>25</sub>H<sub>24</sub>ClN<sub>3</sub>S, MM = 434.01):



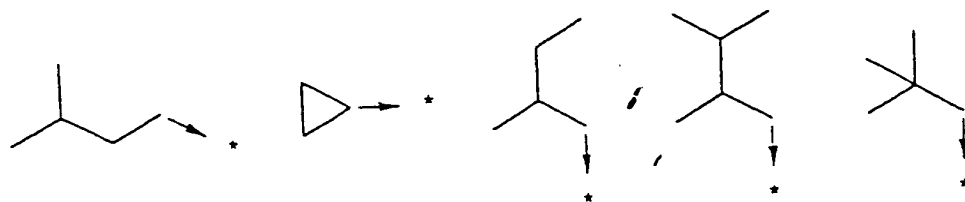
- 5 100 mg (62.9  $\mu$ mol, load of 0.629 mmol/g) of thiourea resin and 2-bromo-4'-chloroacetophenone (30 mg; 125.8  $\mu$ mol; 2 eq.) are dissolved in 1 ml of DMF and heated to 80 °C for 2 hours. The resin is then washed successively with DMF (5 x 1 ml), methanol (5 x 1 ml) and DCM (5 x 1 ml). The resin is agitated in 1 ml of a DCM/trifluoroacetic acid mixture at 50% for one hour and 30 minutes at ambient
- 10 temperature. The resin is rinsed with DCM (5 x 1 ml) and the filtrate evaporated under reduced pressure. The residue, dissolved in methanol, is eluted in a basic alumina cartridge (500 mg, Interchim) in order to quantitatively produce (27.3 mg) the expected product in the form of a solid (UV purity: 97% at 220 nm).
- 15 NMR <sup>1</sup>H (DMSO D<sub>6</sub>, 100 MHz)  $\delta$ : 7.9 (broad s, 2H, NH<sub>2</sub>); 7.53 (d, 2H, J = 8.5 Hz); 7.32-7.15 (m, 7H); 7.08-6.9 (m, 4H); 6.37 (s, 1H, H azole); 4.07 (m, 2H, NCH<sub>2</sub>); 3.03 (m, 2H, NCH<sub>2</sub>); 2.88 (m, 4H). MS/LC: m/z = 435 (M+H)<sup>+</sup>.

A series of 2-arylimino-2,3-dihydrothiazoles was synthesized according to method B with our robotic system (ACT MOS 496):

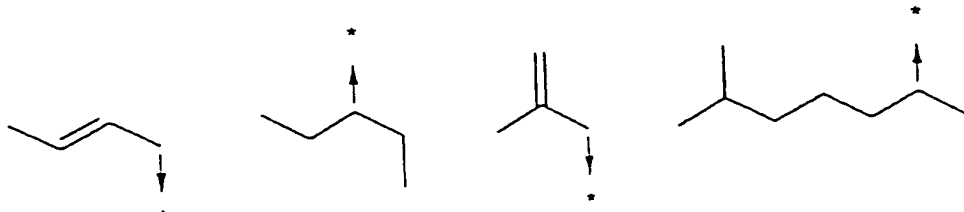
- R1 groups



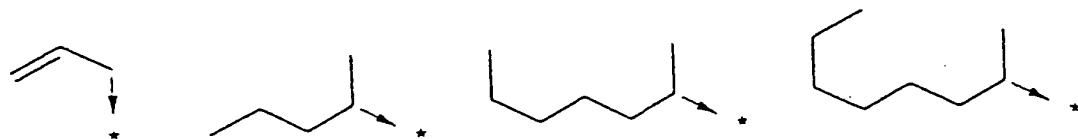
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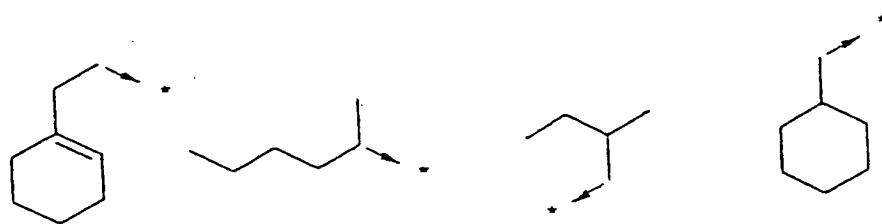
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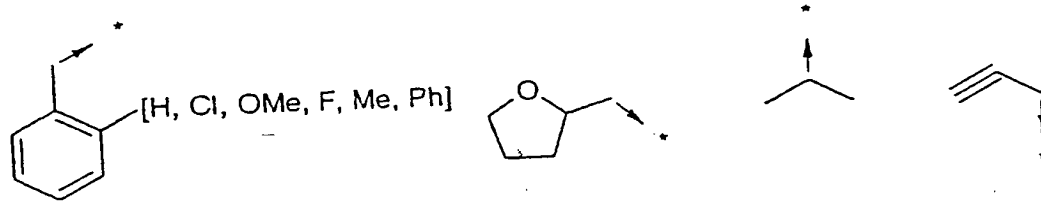
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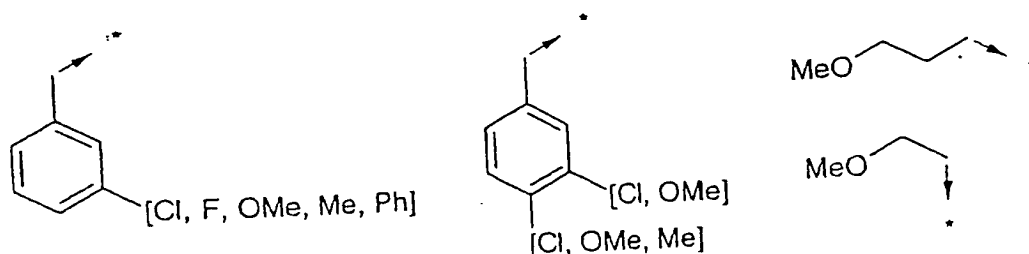
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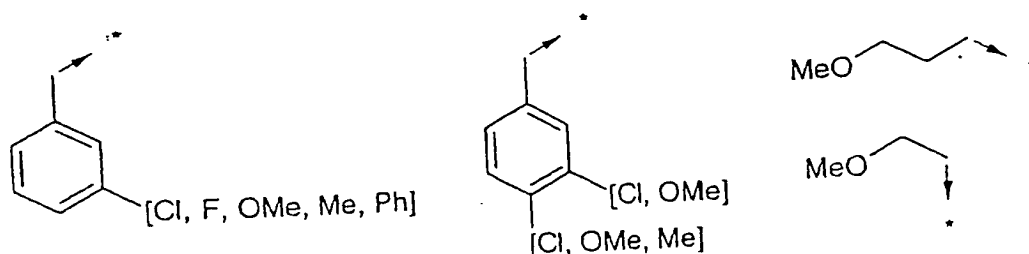
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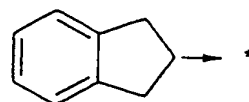
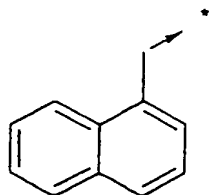
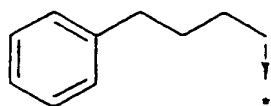
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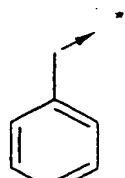
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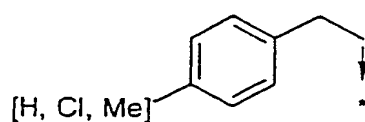
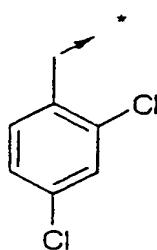
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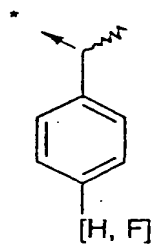


[F, Cl, OMe, Me, Ph]

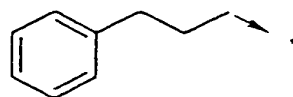
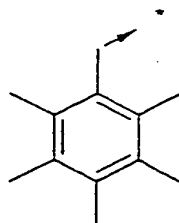
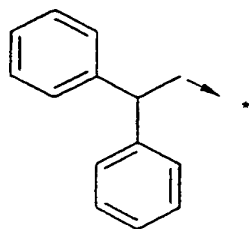


[H, Cl, Me]

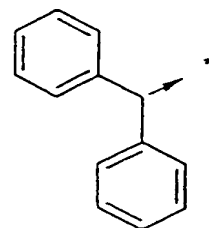
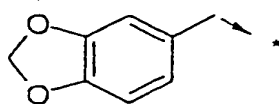
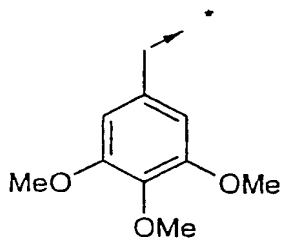
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[H, F]

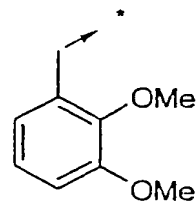
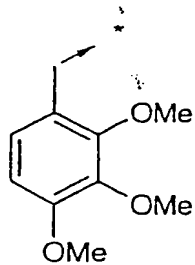
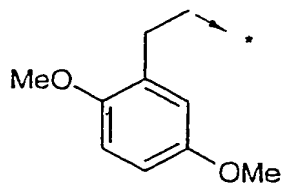


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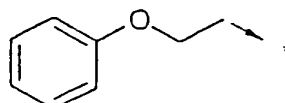
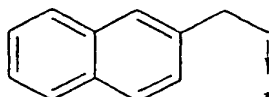
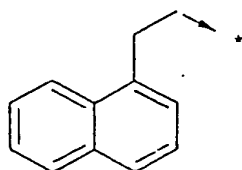


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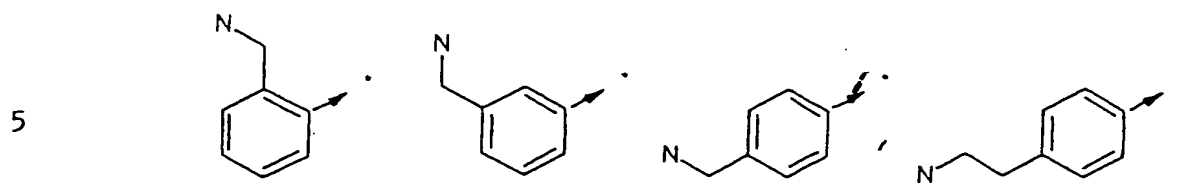


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- R2 groups

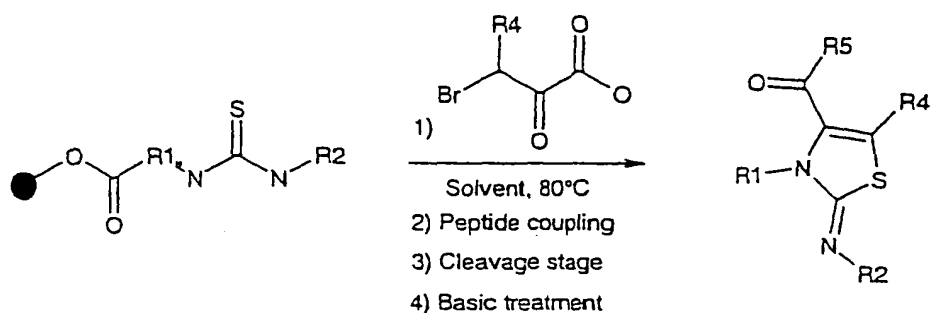


- R3 and R4 groups like those of method A

10

# METHOD C

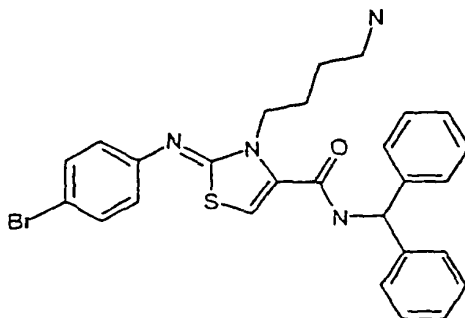
## Synthesis of 2-arylimino-1,3-thiazole-4(3H)-carboxamides



General procedure: a regioselective cyclization stage using  $\alpha$ -bromopyruvic acid (2-5 eq.) is carried out starting from the thiourea resin prepared in the method A in aprotic solvents such as dioxane or DMF at 80 °C for 2-3 hours. The resin is then washed successively with DMF, methanol and DCM then dried under reduced pressure. The peptide coupling (Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillesen, D. *Tetrahedron Lett.* 989, 30, 1927-1930) takes place in DMF at ambient temperature for 1-24 hours with different standard coupling agents (4-5 eq.) such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), a DIC/N-hydroxybenzotriazole (HOBt) mixture, benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate (PyBOP), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) or 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and aminated compounds (4-5 eq.). The 2-arylimino-1,3-thiazole-4(3H)-carboxamide resin is cleaved by treatment under acid conditions (DCM/trifluoroacetic acid at 50%) for 1-2 hours then rinsed with DCM. The solvent is evaporated off and the free base is isolated after treatment under basic conditions (saturated solution of sodium hydrogen carbonate), extraction is carried out with DCM or elution with methanol in a basic alumina cartridge (500 mg, Interchim).

### Example 3

3-(4-aminobutyl)-N-benzhydryl-2-[(4-bromophenyl)imino]-1,3-thiazole-4(3H)-carboxamide  
(C<sub>27</sub>H<sub>27</sub>BrN<sub>4</sub>OS, MM = 535.51):



5

50 mg (27.5  $\mu$ mol, load of 0.55 mmol/g) of carboxylic acid resin is activated for 15 minutes with 14.8 mg (0.11 mmol, 4 eq.) of N-hydroxybenzotriazole and 35.3 mg (0.11 mmol, 4 eq.) of TBTU in 800  $\mu$ l of anhydrous DMF. 20.7 mg (0.11 mmol, 4 eq.) of aminodiphenylmethane dissolved in 200  $\mu$ l of anhydrous DMF is then added and the resin is filtered after agitation overnight at ambient temperature. A sequential washing with DMF (5 x 1 ml), methanol (5 x 1 ml) and DCM (5 x 1 ml) produces a resin which is treated for one hour and 30 minutes under acid conditions (DCM/trifluoroacetic acid at 50 %). The resin is rinsed with DCM (5 x 1 ml) and the filtrate evaporated under reduced pressure. The residue, taken up in methanol, is eluted in a basic alumina cartridge (500 mg, Interchim) in order to produce a pale yellow solid (8.2 mg; yield of 55.7 %; UV purity of 94 % at 220 nm).

15

NMR <sup>1</sup>H (DMSO D6, 100 MHz,  $\delta$ ): 9.6 (d; 1H; J = 8.6Hz; NH); 7.49 (d; 2H; J = 8.6 Hz); 7.35 (s; 10H); 6.92 (s; 1H; H azole); 6.91 (d; 2H; J = 8.5 Hz); 6.27 (d; 1H; J = 8.5 Hz; NHCH); 4.02 (m; 2H; NCH<sub>2</sub>); 3.45 (broad m; 2H+2H; NH<sub>2</sub> and NCH<sub>2</sub>); 1.55–1.24 (broad m; 4H). MS/LC: m/z = 535 (M+H).

20

A series of 2-arylimino-1,3-thiazole-4(3H)-carboxamides was synthesized according to method C using our robotic system (ACT MOS 496):

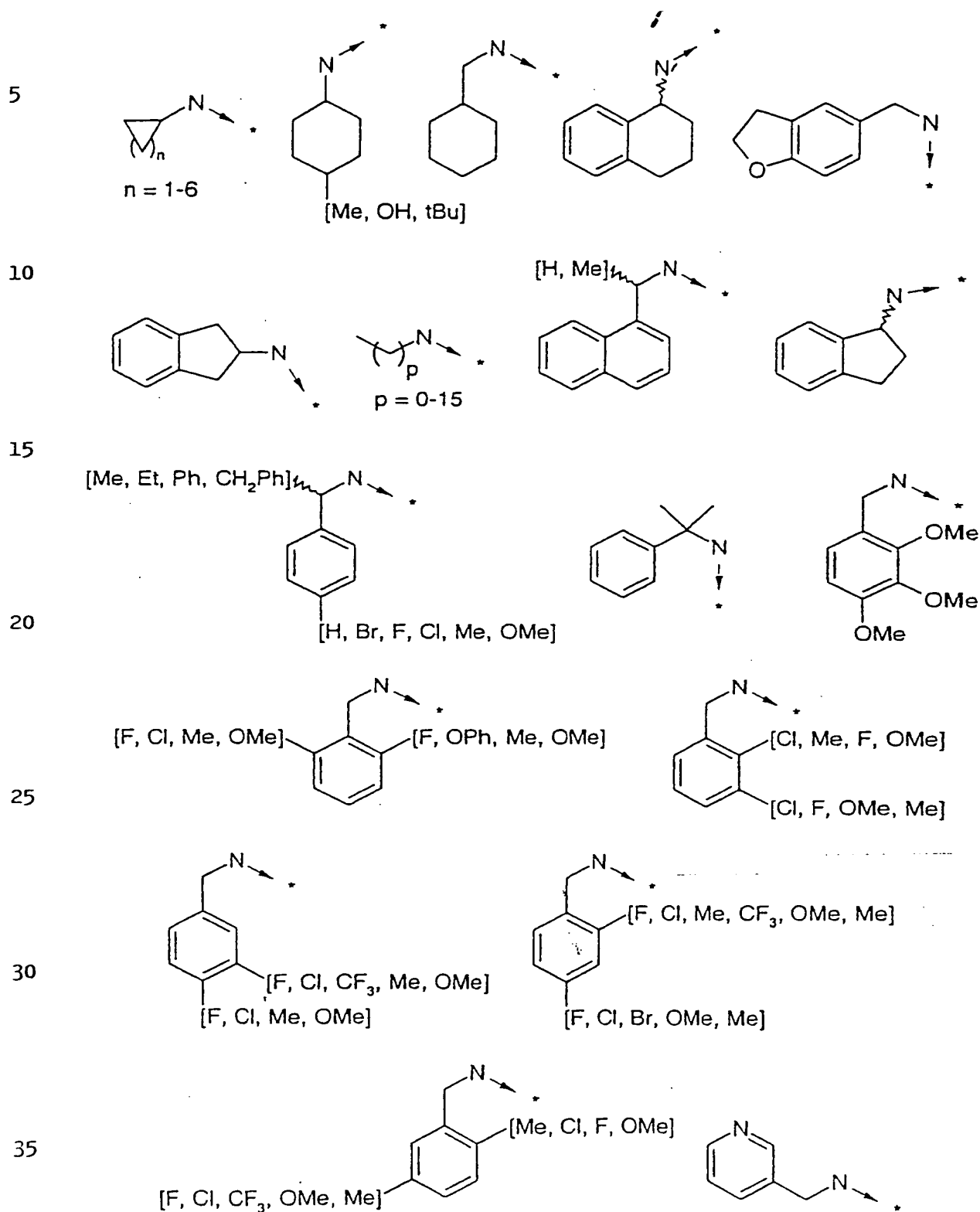
- R1 and R2 groups already described in method A;

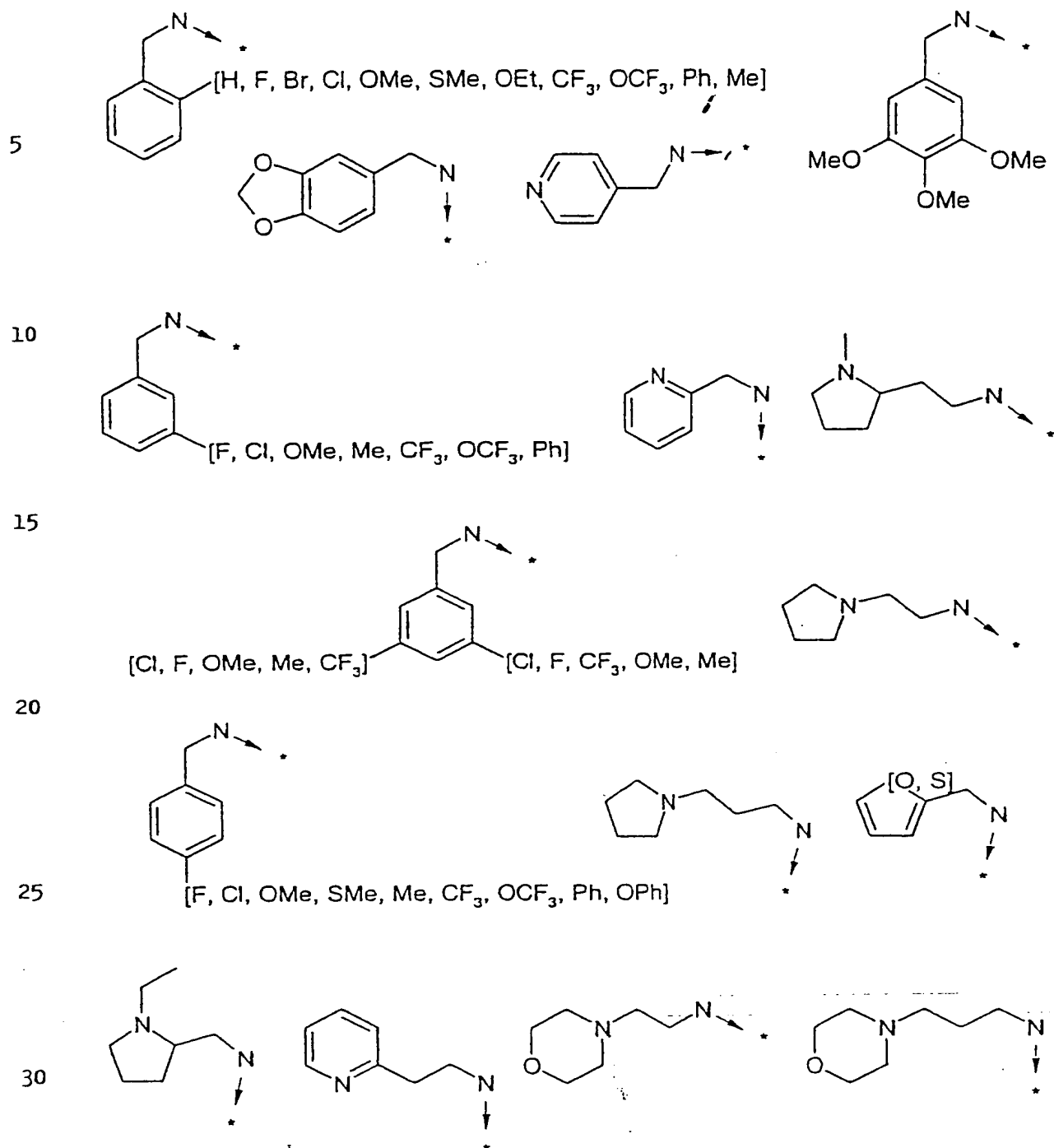
- R3 = -CO-R5;

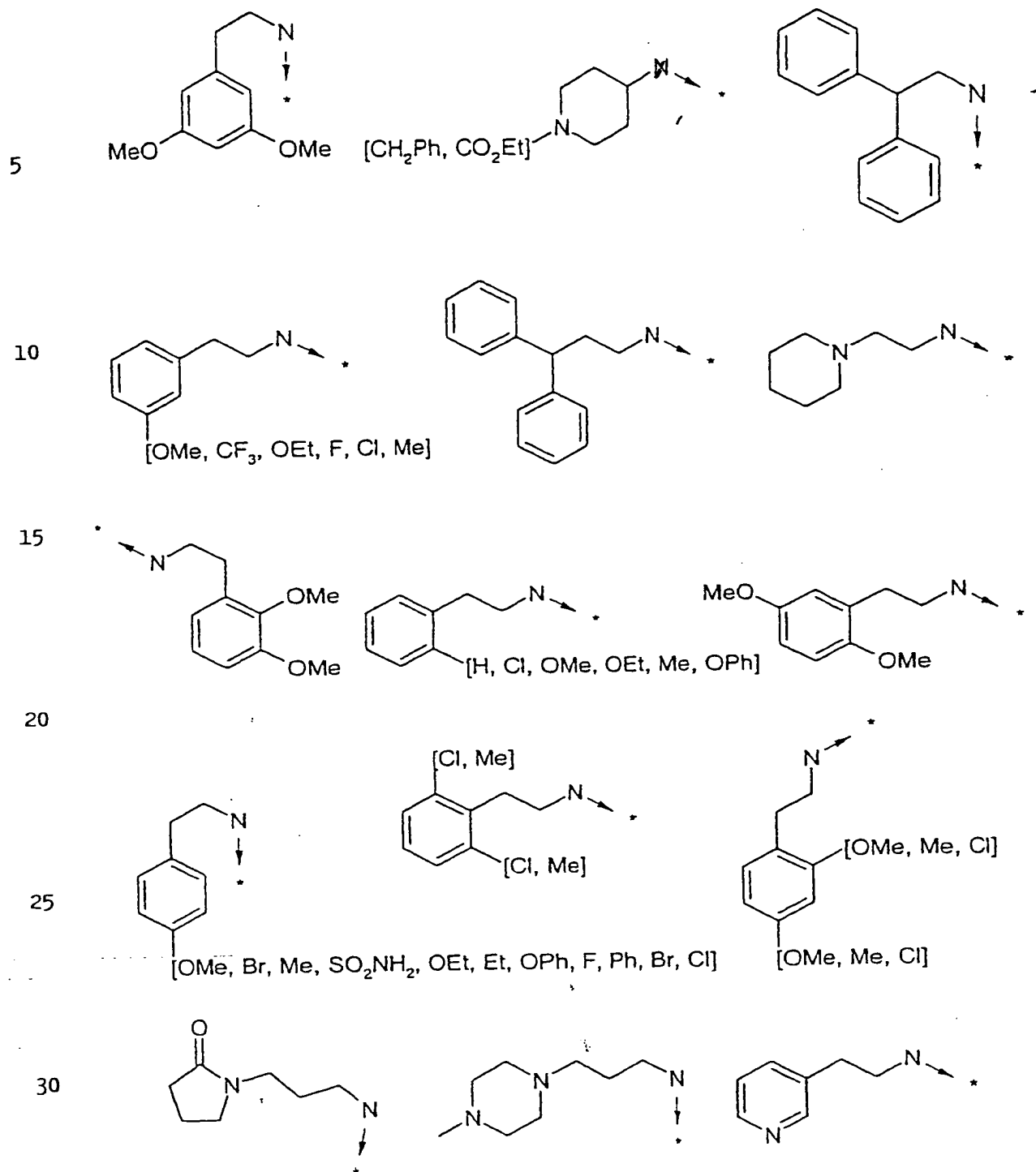
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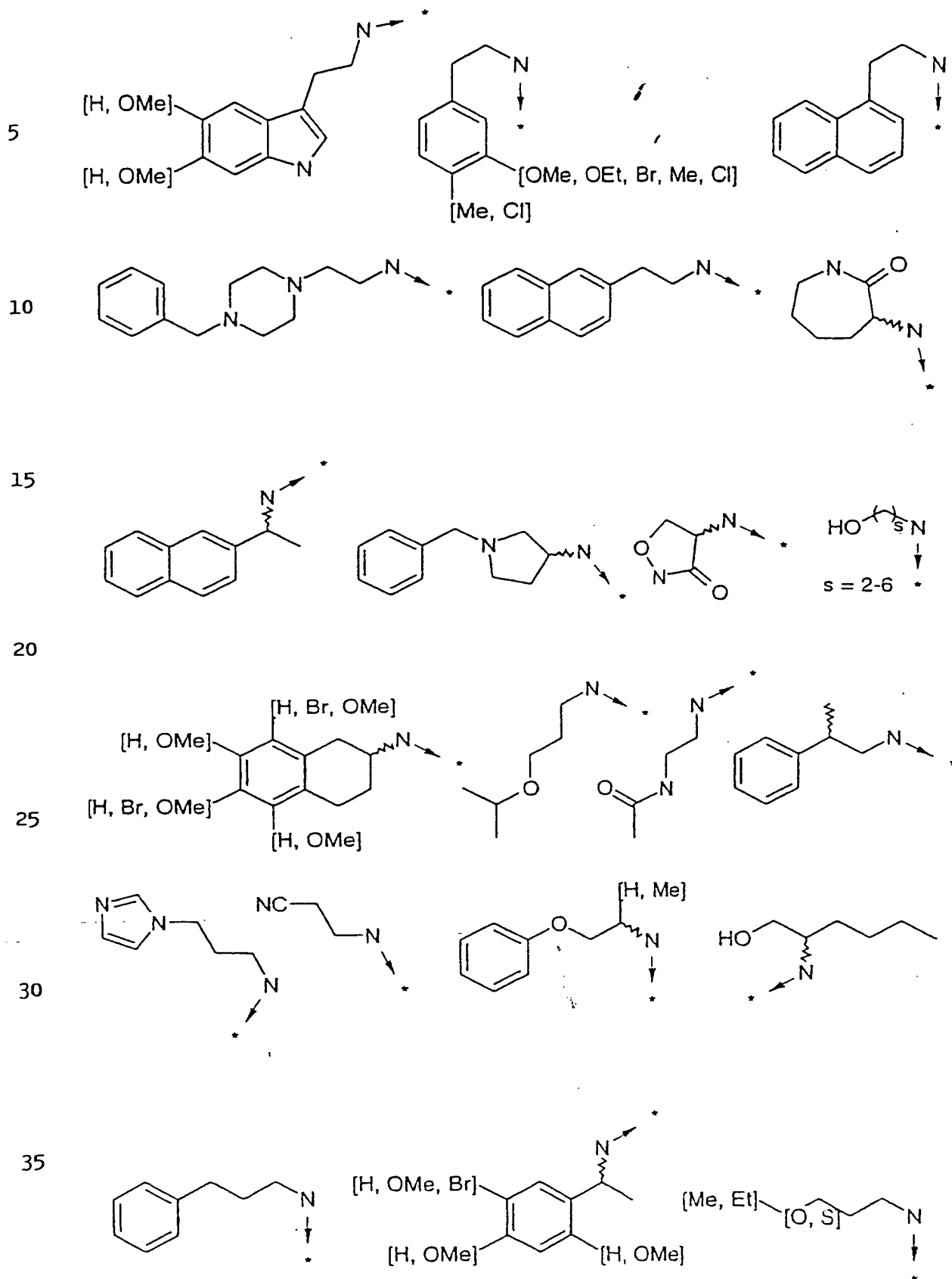
- R4 = H;

- R5 groups

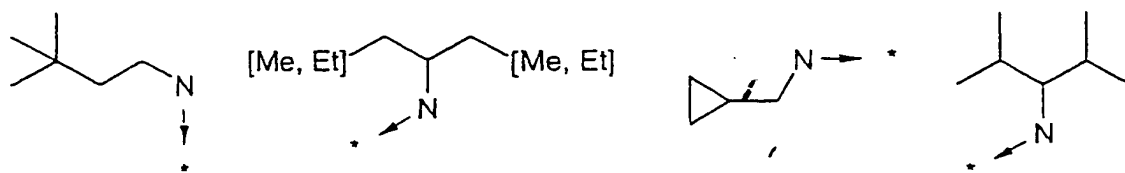




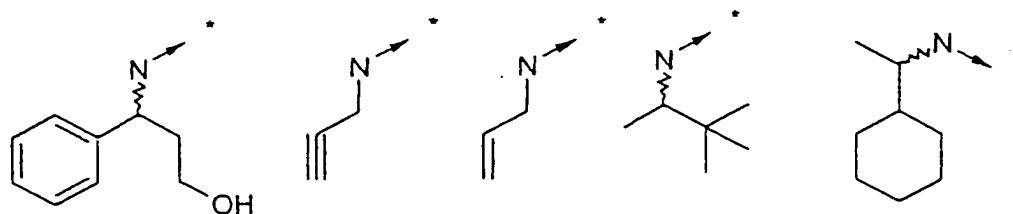




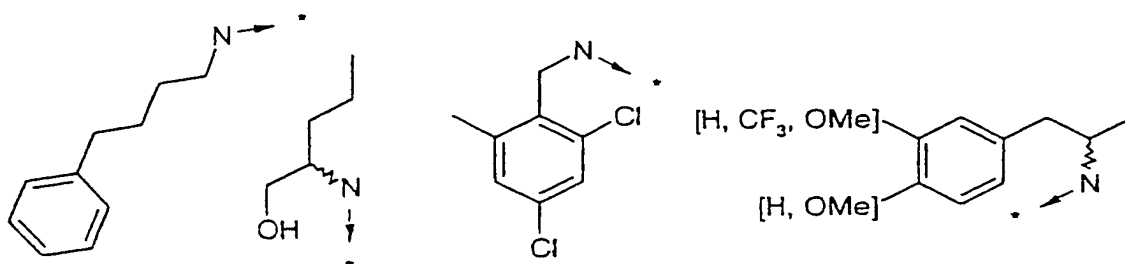
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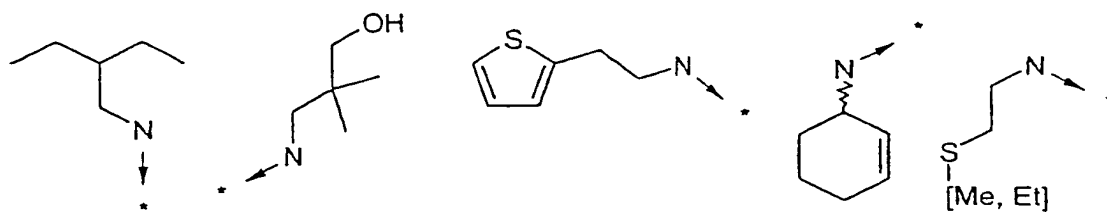
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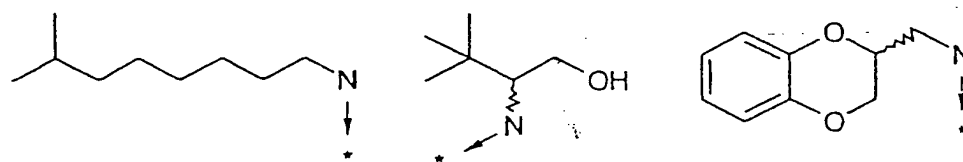
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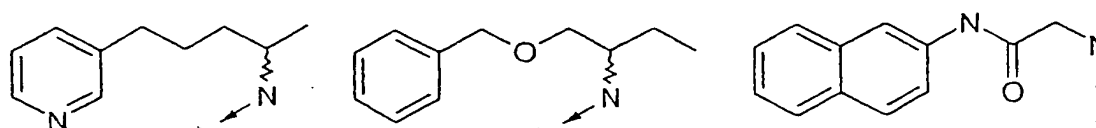
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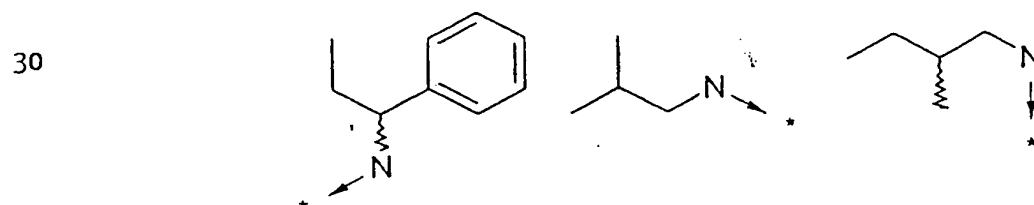
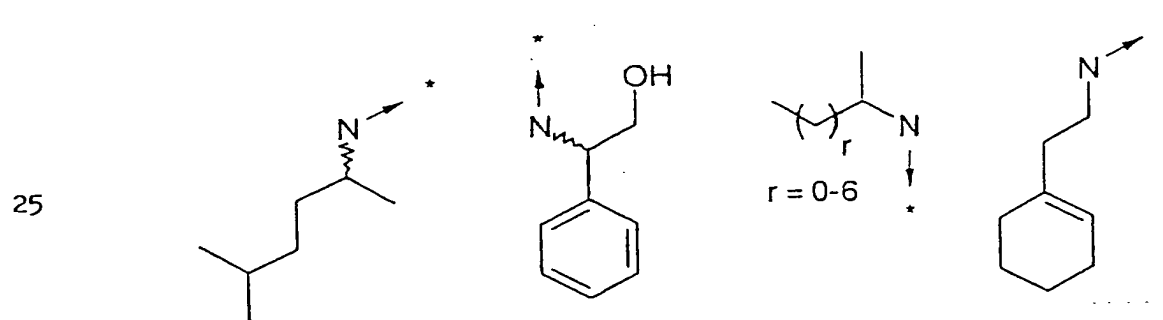
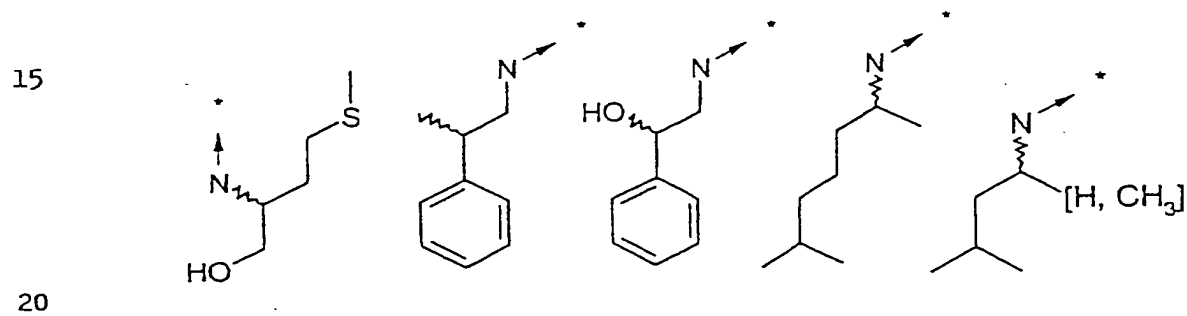
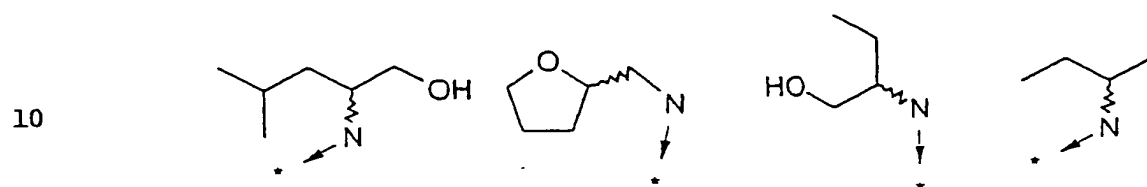
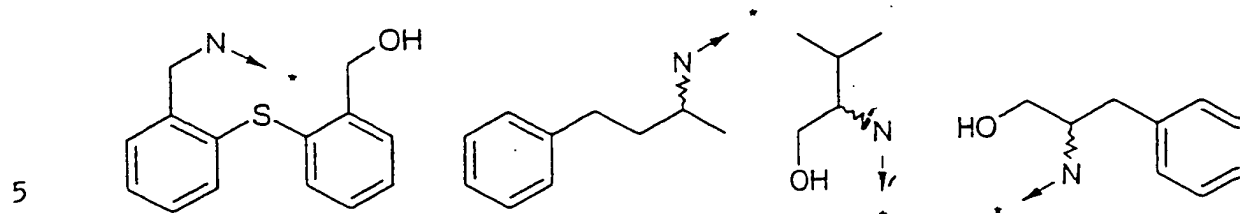


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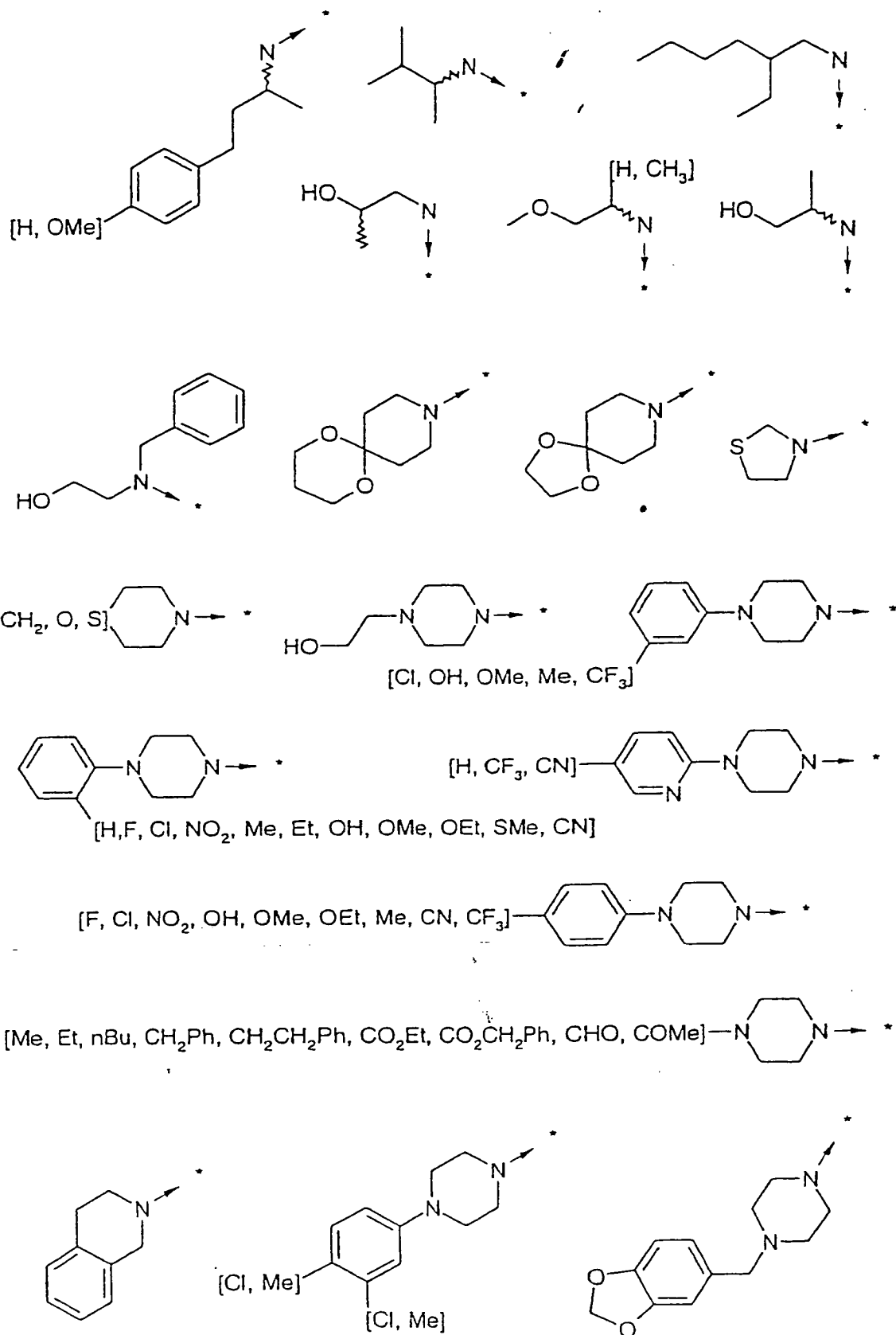
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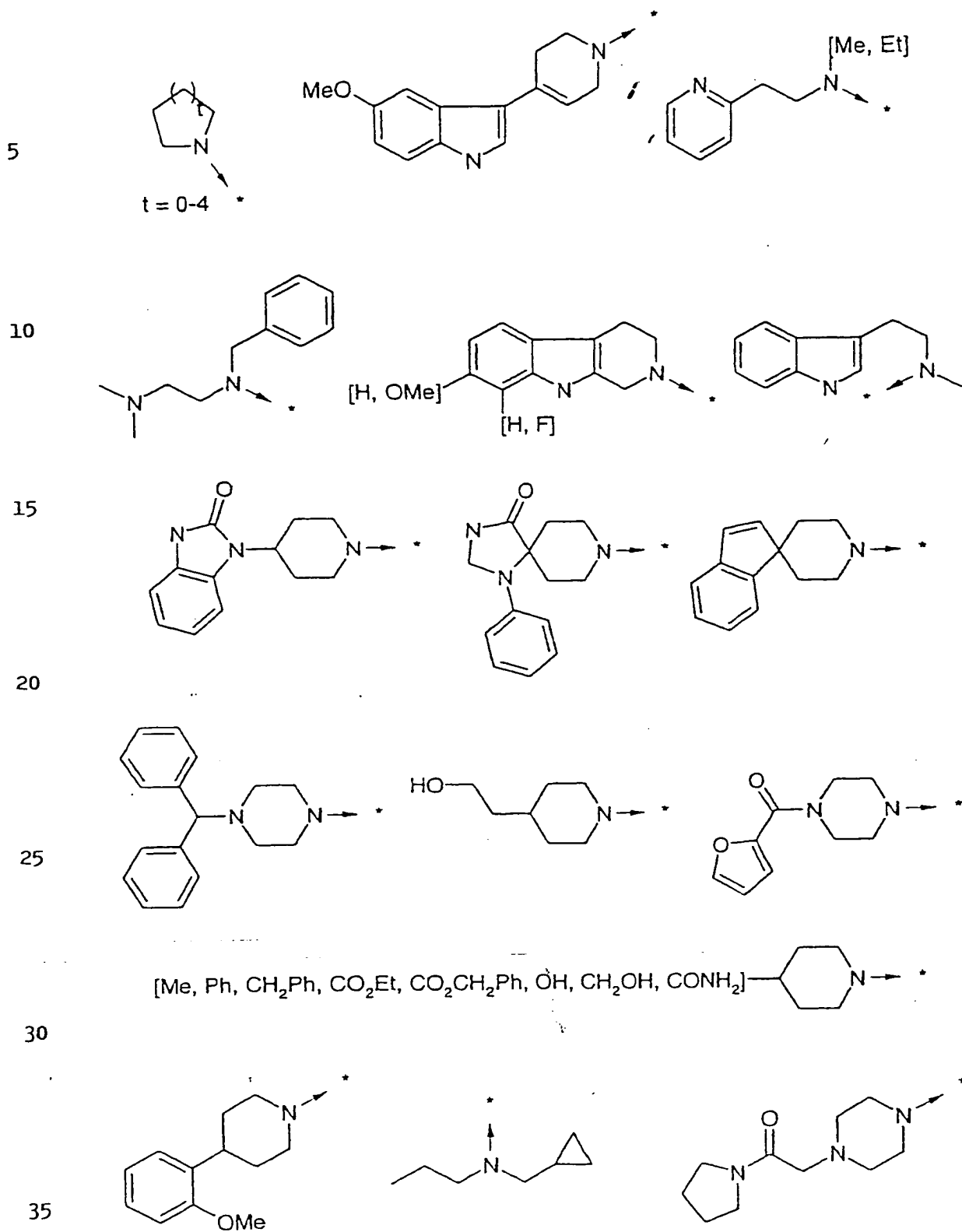
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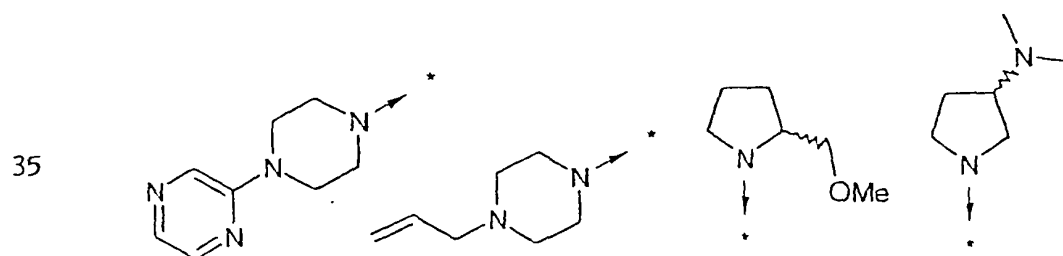
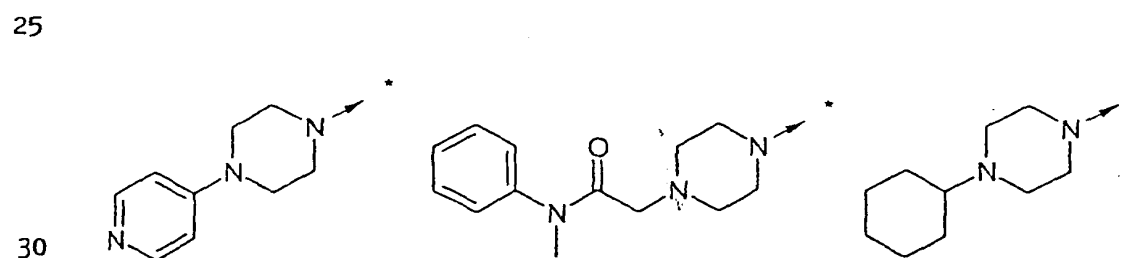
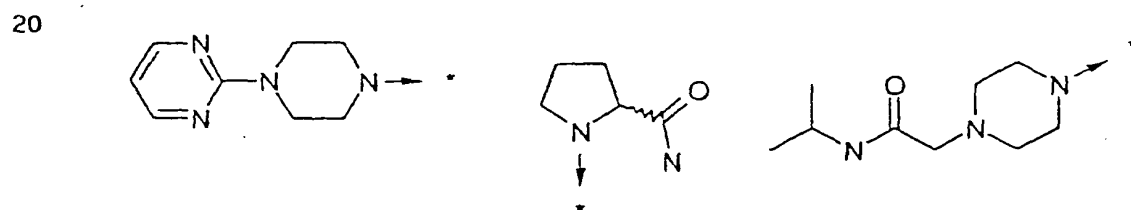
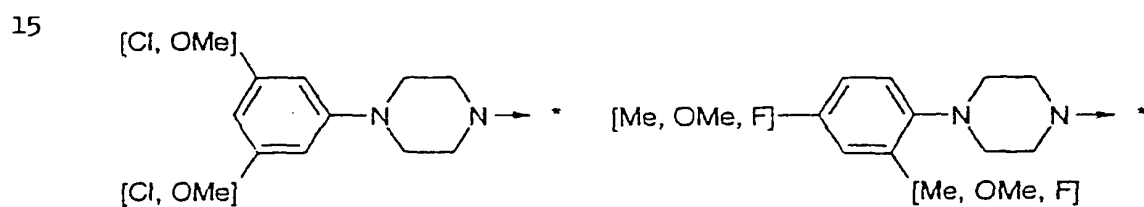
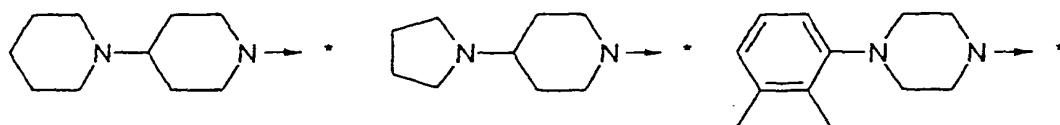
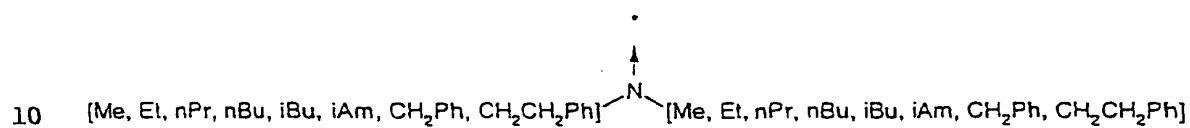
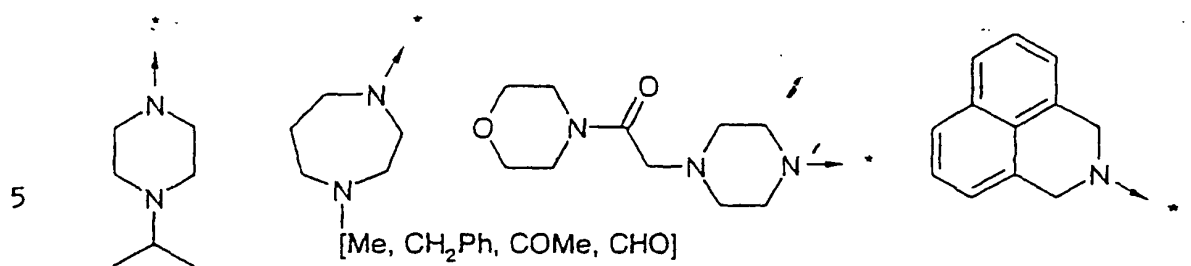
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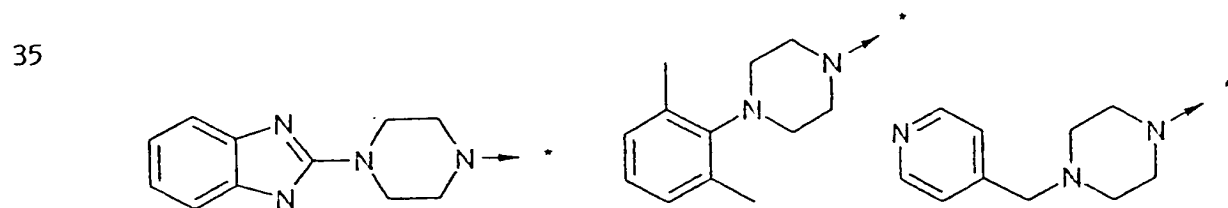
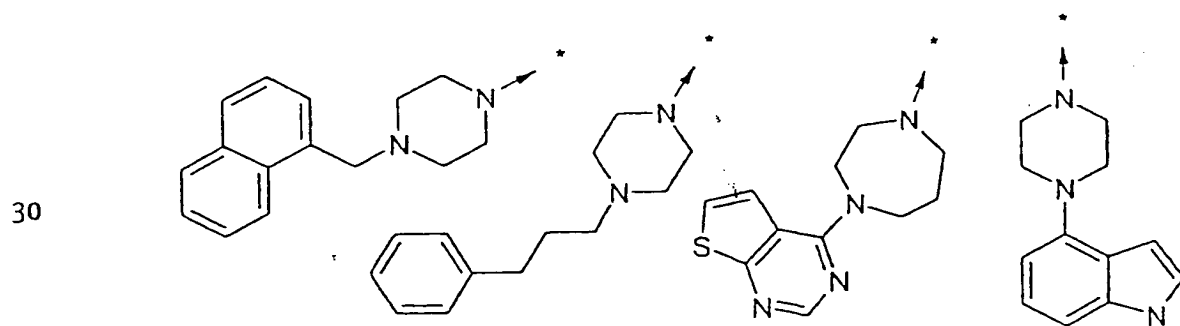
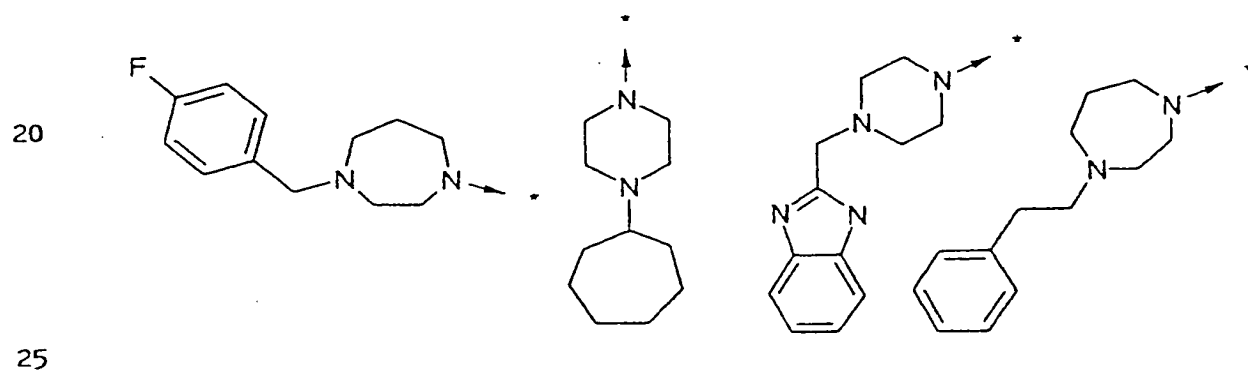
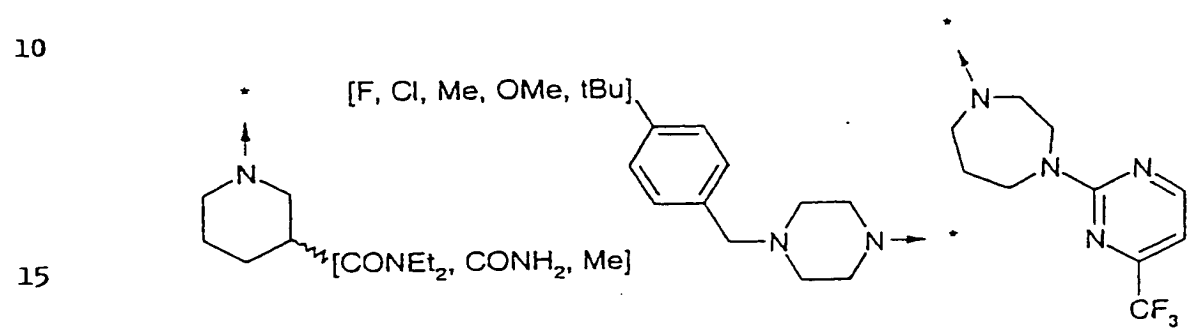
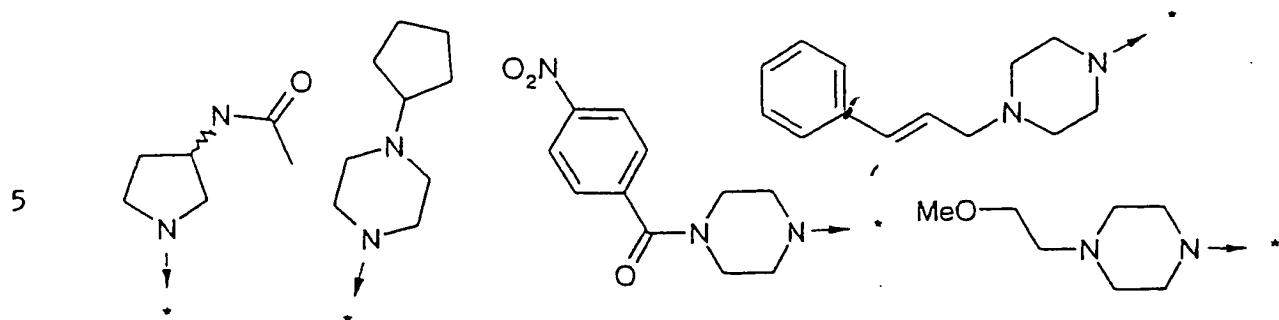
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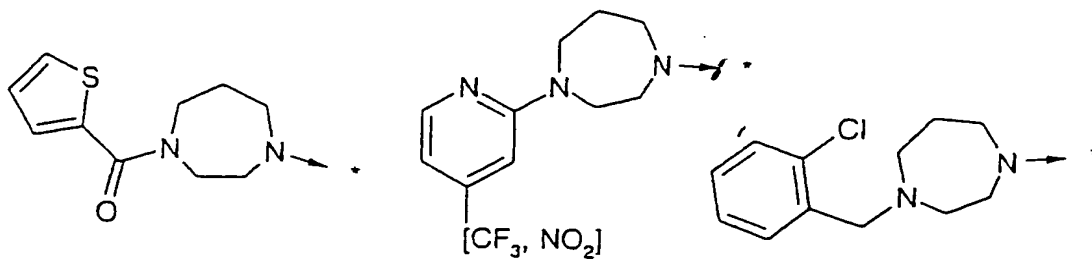




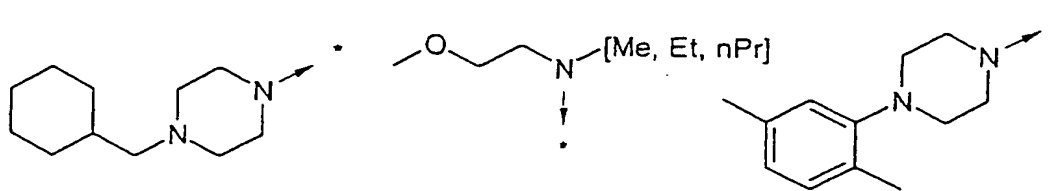




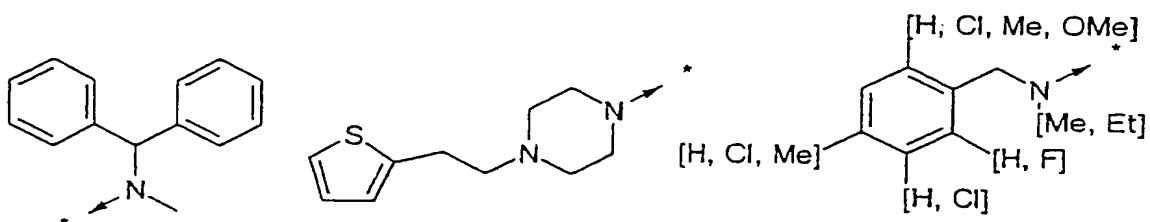
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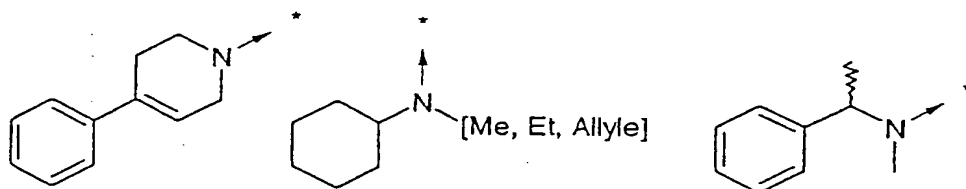
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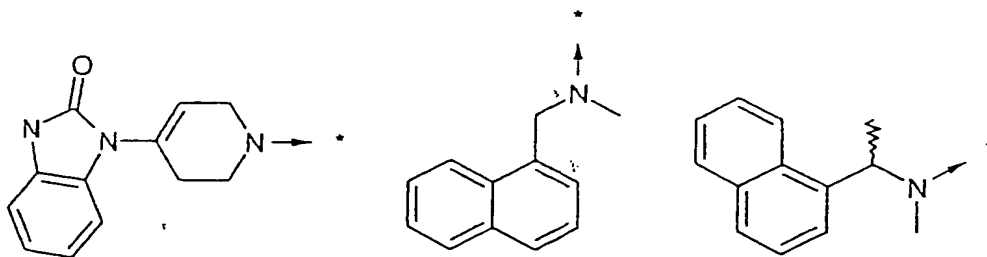
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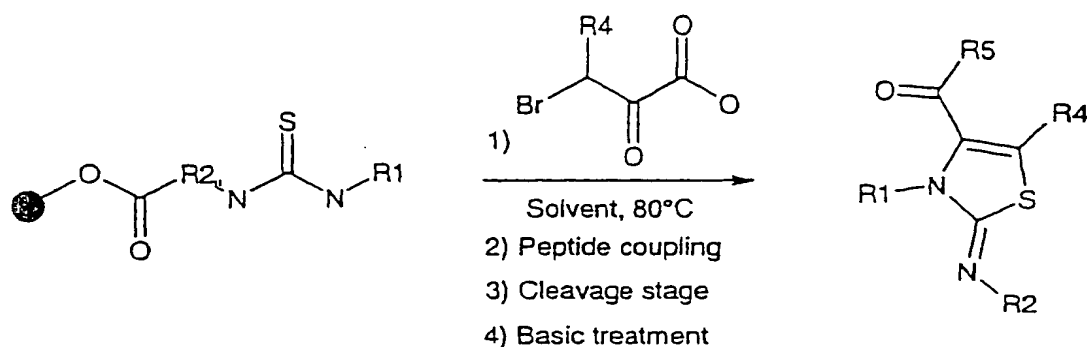


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# METHOD D

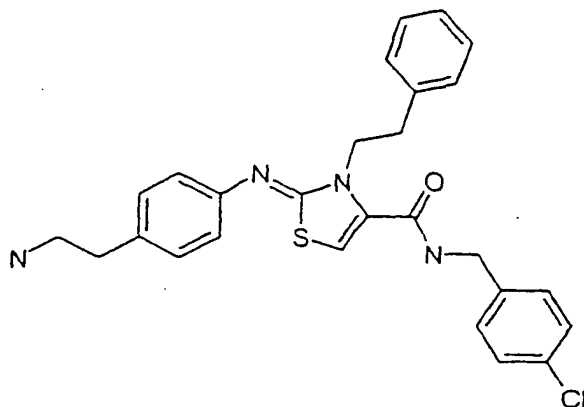
## Synthesis of 2-arylimino-1,3-thiazole-4(3*H*)-carboxamides



General procedure: a regioselective cyclization stage using  $\alpha$ -bromopyruvic acid (2-5 eq.) is carried out starting from the thiourea resin prepared in method B in aprotic solvents such as dioxane or DMF at 80 °C for 2-3 hours. The resin is then successively washed with DMF, methanol and DCM then dried under reduced pressure. The peptide coupling (Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillesen, D. *Tetrahedron Lett.* 1989, 30, 1927-1930) takes place in DMF at ambient temperature for 1-24 hours with different standard coupling agents (4-5 eq.) such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), a DIC/*N*-hydroxybenzotriazole (HOBt) mixture, benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate (PyBOP), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) or 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and aminated compounds (4-5 eq.). The 2-arylimino-1,3-thiazole-4(3*H*)-carboxamide resin is cleaved by treatment under acid conditions (DCM/trifluoroacetic acid at 50%) for 1-2 hours then rinsed with DCM. The solvent is evaporated off and the free base is isolated after treatment under basic conditions (saturated solution of sodium hydrogen carbonate) followed by an extraction with DCM or elution with methanol in a basic alumina cartridge (500 mg, Interchim).

Example 4

(2Z)-2-([4-(2-aminoethyl)phenyl]imino)-N-(4-chlorobenzyl)-3-(2-phenylethyl)-2,3-dihydro-1,3-thiazole-4-carboxamide  
(C<sub>27</sub>H<sub>27</sub>ClN<sub>4</sub>OS, MM = 491.05):



Phenylethylisothiocyanate (310 mg; 1.9 mmol; 10 eq.) in 3 ml of dimethylformamide is added to 200 mg (190  $\mu$ mol, load of 0.946 mmol/g) of aminated resin (see Preparation 20). Agitation overnight at ambient temperature produces a negative Kaiser ninhydrin test. The resin is then successively washed with DMF (5 x 3 ml) and DCM (5 x 3 ml) then dried under vacuum for one hour before adding bromopyruvic acid (63.4 mg; 380  $\mu$ mol; 2 eq.) diluted beforehand in 3 ml of dimethylformamide. The mixture is agitated for 2.5 hours at 80°C. The resin is filtered and washed with DMF (5 x 3 ml), methanol (3 x 3 ml) then DCM (5 x 3 ml). The carboxylic acid resin is preactivated for 1 hour with 244 mg (0.76 mmol; 4 eq.) of TBTU diluted in 2 ml of anhydrous DMF. 110 mg (0.76 mmol; 4 eq.) of 4-chlorobenzylamine dissolved in 1 ml of anhydrous DMF is then added and the resin is filtered after agitation overnight at ambient temperature. Sequential washing with DMF (5 x 3 ml), methanol (3 x 3 ml) and DCM (3 x 3 ml) produces a resin which is treated for one hour and 30 minutes under acid conditions (DCM/trifluoroacetic acid at 50 %). The resin is rinsed with DCM (5 x 1 ml) and the filtrate evaporated under reduced pressure. The residue, taken up in DCM, is neutralized with a saturated solution of sodium hydrogen carbonate in order to produce after evaporation a solid (38.2 mg; yield of 41%; UV purity of 90% at 210 nm).  
NMR <sup>1</sup>H (DMSO D<sub>6</sub>, 400 MHz,  $\delta$ ): 9.1 (m, 1H); 7.39 (d, 2H, J = 8.4 Hz); 7.33 (d, 2H, J = 8.4 Hz); 7.25 (q, 2H, J = 6.8 Hz); 7.19 (q, 1H, J = 7.2 Hz); 7.11 (m, 4H); 6.8 (d, 2H, J = 8 Hz); 6.75 (s, 1H, Hazole); 4.34 (d, 2H, J = 6 Hz); 4.27 (t, 2H, J = 6.8 Hz); 3.14 (m, 1H); 2.89 (t, 2H, J = 6.8 Hz); 2.73 (t, 1H, J = 7.2 Hz); 2.62 (m, 2H). MS/LC: m/z = 491.24 (M+H)<sup>+</sup>.

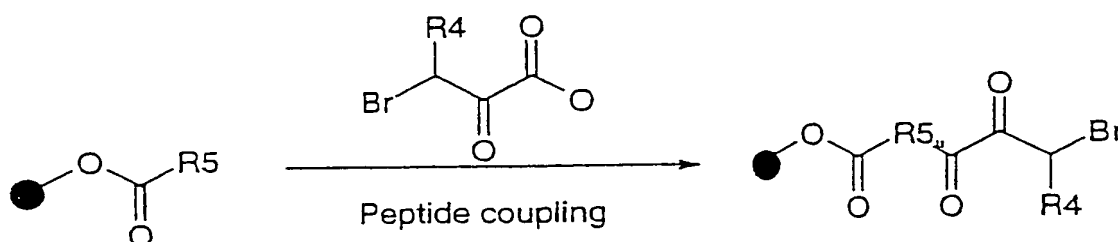


A series of 2-arylimino-1,3-thiazole-4(3*H*)-carboxamides was synthesized according to method D using our robotic system (ACT MOS 496):

- R1 and R2 groups already described in method B
- R3 = -CO-R5
- R4 = H
- R5 groups already described in method C.

#### METHOD E

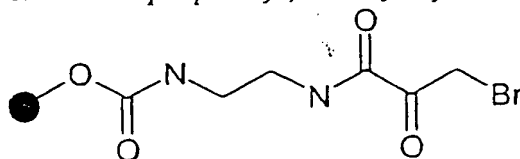
Preparation of monoprotected diamine resin functionalized with  $\alpha$ -bromopyruvic acid



General procedure: the monoprotected symmetrical primary or secondary diamine resin (the preparation of which is already described in method A) is functionalized by peptide coupling with  $\alpha$ -bromopyruvic acid (10 eq.), DIC (10 eq.) and HOBt (10 eq.) in a solvent such as DMF at ambient temperature. The resin is washed successively with DMF then with DCM after 2 to 24 hours of agitation before being dried under vacuum. The negative Kaiser ninhydrin test indicates a complete functionalization.

#### Preparation 22

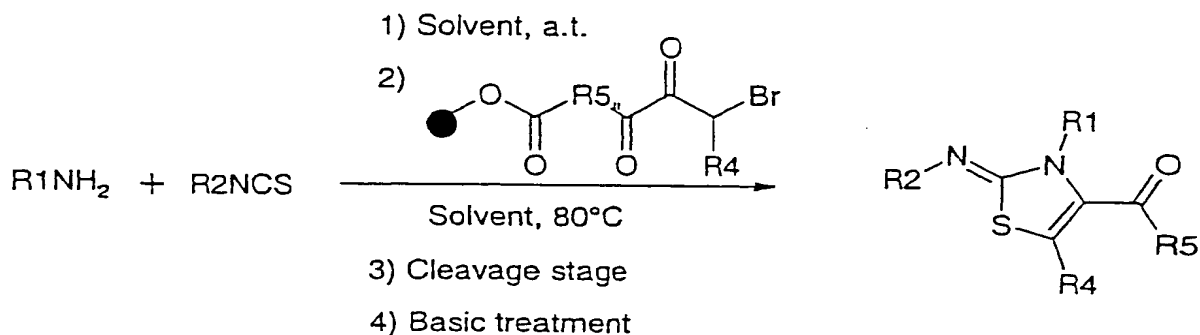
*N*-carbamate of 2-[(3-bromo-2-oxopropanoyl)amino]ethyl Wang resin



HOBt (0.93 g, 6.88 mmol) and  $\alpha$ -bromopyruvic acid (1.18 g, 6.88 mmol) are dissolved in 28 ml of DMF (0.5 M). DIC (1.07 ml; 6.88 mmol) is then added by syringe to activate the acid. The mixture is agitated for approximately 15 minutes at ambient temperature before adding it to the ethylene diamine Wang resin *N*-carbamate (0.8 g; 0.688 mmol; load rate 0.86 mmol/g). After agitation for 3 hours at ambient

temperature, the Kaiser ninhydrin test being negative, the resin is filtered and washed successively with DMF (5 x 20 ml) then with DCM (5 x 20 ml) before being dried under vacuum. An ochre resin (0.812 g) is obtained with a load rate of 0.525 mmol/g<sup>-</sup> calculated from elemental analysis of the bromine.

5 Synthesis of 2-arylimino-1,3-thiazole-4(3*H*)-carboxamides

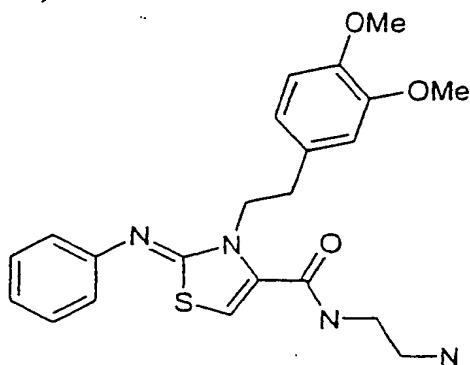


General procedure: formation of the thiourea is carried out in a solvent such as DMF or dioxane by mixing an equimolar quantity of primary amine and aromatic or heteroaromatic isothiocyanate. After agitation for 2 to 24 hours at ambient temperature, the thiourea (2 to 5 eq.) is added to the functionalized resin then heated at 80°C for 2 to 4 hours. The 2-arylimino-1,3-thiazole-4(3*H*)-carboxamide resin is cleaved by treatment under acid conditions (DCM/trifluoroacetic acid at 50%) for 1-2 hours then rinsing with DCM. The solvent is evaporated off and the free base isolated after treatment under basic conditions (saturated solution of sodium hydrogen carbonate), extraction with DCM or elution with methanol in a basic alumina cartridge (500 mg, Interchim).

Example 5

(2Z)-N-(2-aminoethyl)-3-[2-(3,4-dimethoxyphenyl)ethyl]-2-(phenylimino)-2,3-dihydro-1,3-thiazole-4-carboxamide

(C<sub>22</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub>S, MM = 426.54):



18  $\mu$ l (105  $\mu$ mol; 2 eq.) of  $\beta$ -(3,4-dimethoxyphenyl)ethylamine and 12.6  $\mu$ l (105  $\mu$ mol; 2 eq.) of phenylisothiocyanate are agitated in 1 ml of DMF for 18 hours. The thiourea is added to 100 mg (52.5  $\mu$ mol; load rate of 0.525 mmol/g) of resin (Preparation 22) and the mixture heated at 80°C for 3 hours. The resin is then filtered then washed successively with DMF (5 x 1 ml), methanol (5 x 1 ml) then DCM (5 x 1 ml). The resin is dried under vacuum before adding 1 ml of a 50% DCM/TFA mixture. Agitation is carried out for 1.5 hours at ambient temperature, the resin is filtered and rinsed with DCM. The residue recovered after evaporation is then eluted with methanol in a basic alumina cartridge in order to isolate 22.2 mg (quantitative yield; UV purity of 93.4 % at 230 nm) of a brown solid corresponding to the free amine.

NMR <sup>1</sup>H (DMSO D<sub>6</sub>, 100 MHz,  $\delta$ ): 8.42 (m, 1H, NH); 7.32 (t, 2H, J = 7.1 Hz); 7.08-6.63 (m, 6H); 5.76 (s, 1H, Hazole); 4.31 (t, 2H, J = 6.6 Hz); 3.72 (s, 6H, OCH<sub>3</sub>); 3.32 (broad s, 2H); 3.17 (m, 2H); 2.89 (m, 2H); 2.62 (m, 2H). MS/LC: m/z = 427.17 (M+H)<sup>+</sup>.

A series of 2-arylimino-1,3-thiazole-4(3*H*)-carboxamides was synthesized according to method E using our robotic system (ACT MOS 496):

- R1 groups:

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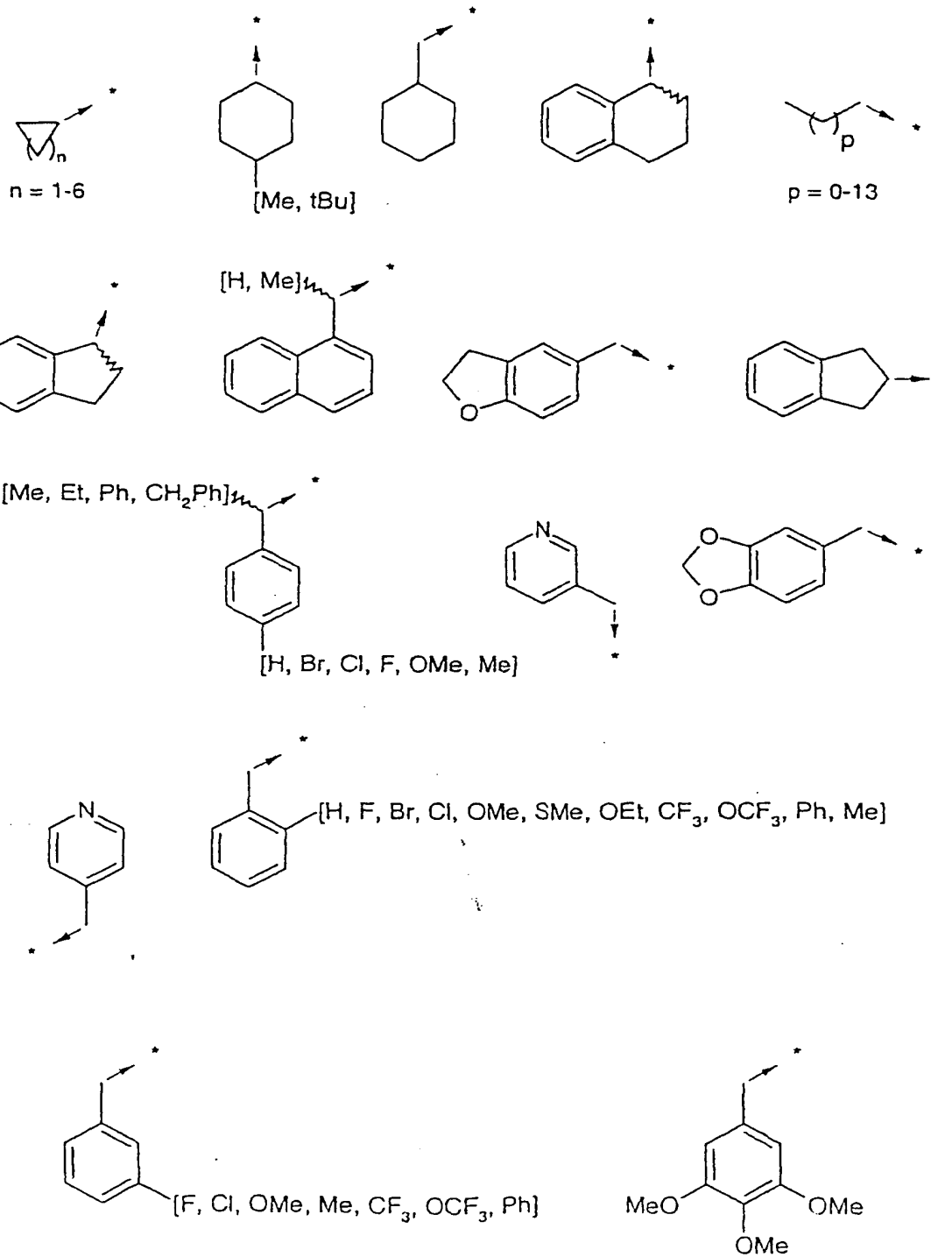
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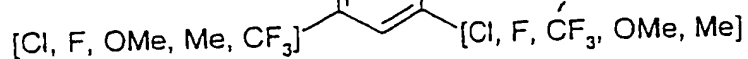
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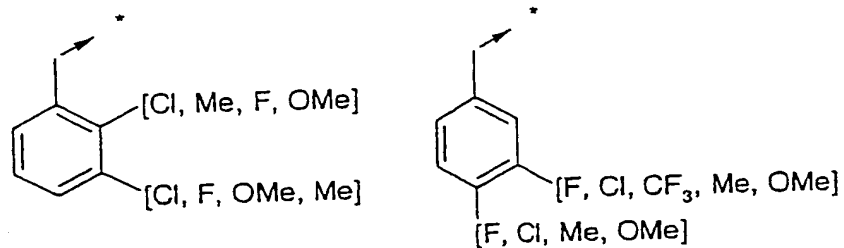
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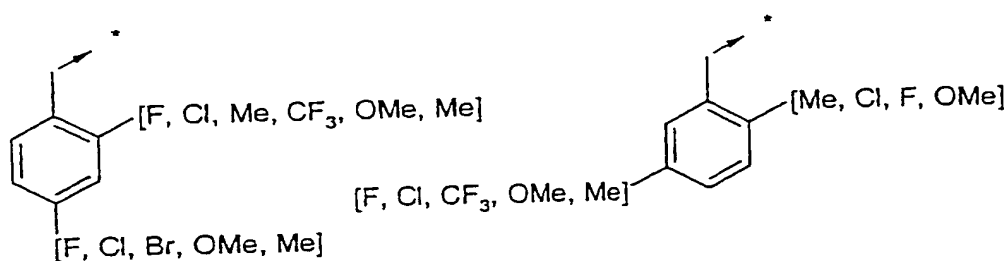
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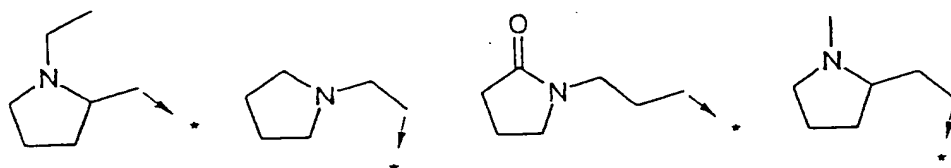
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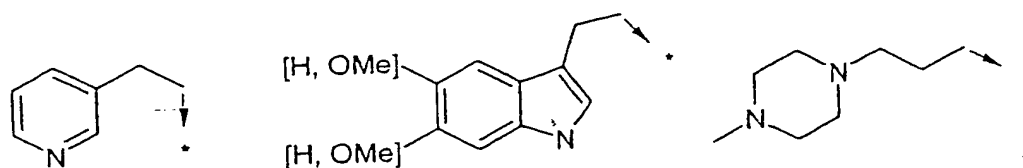
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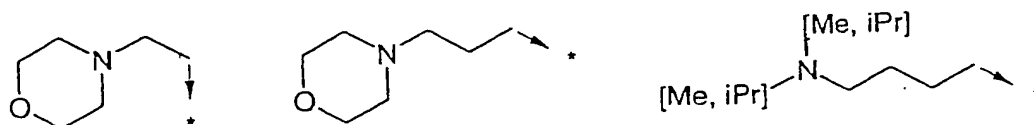
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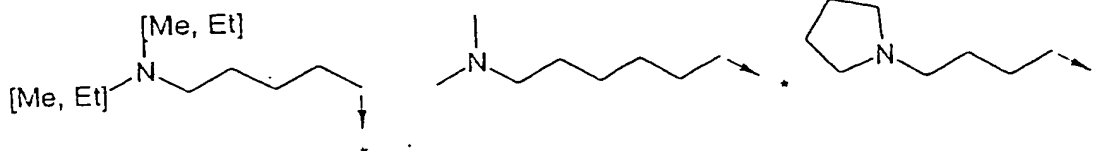
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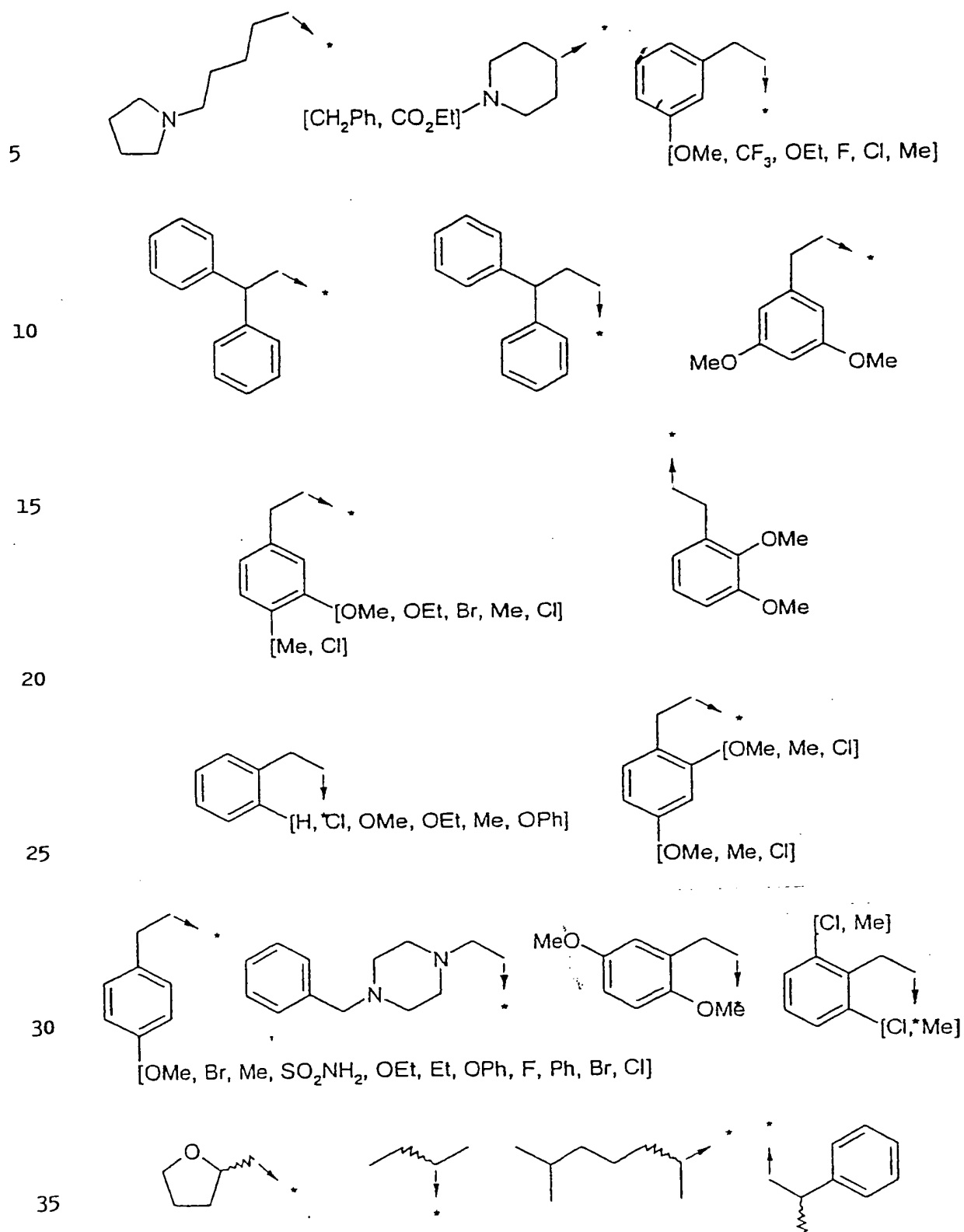


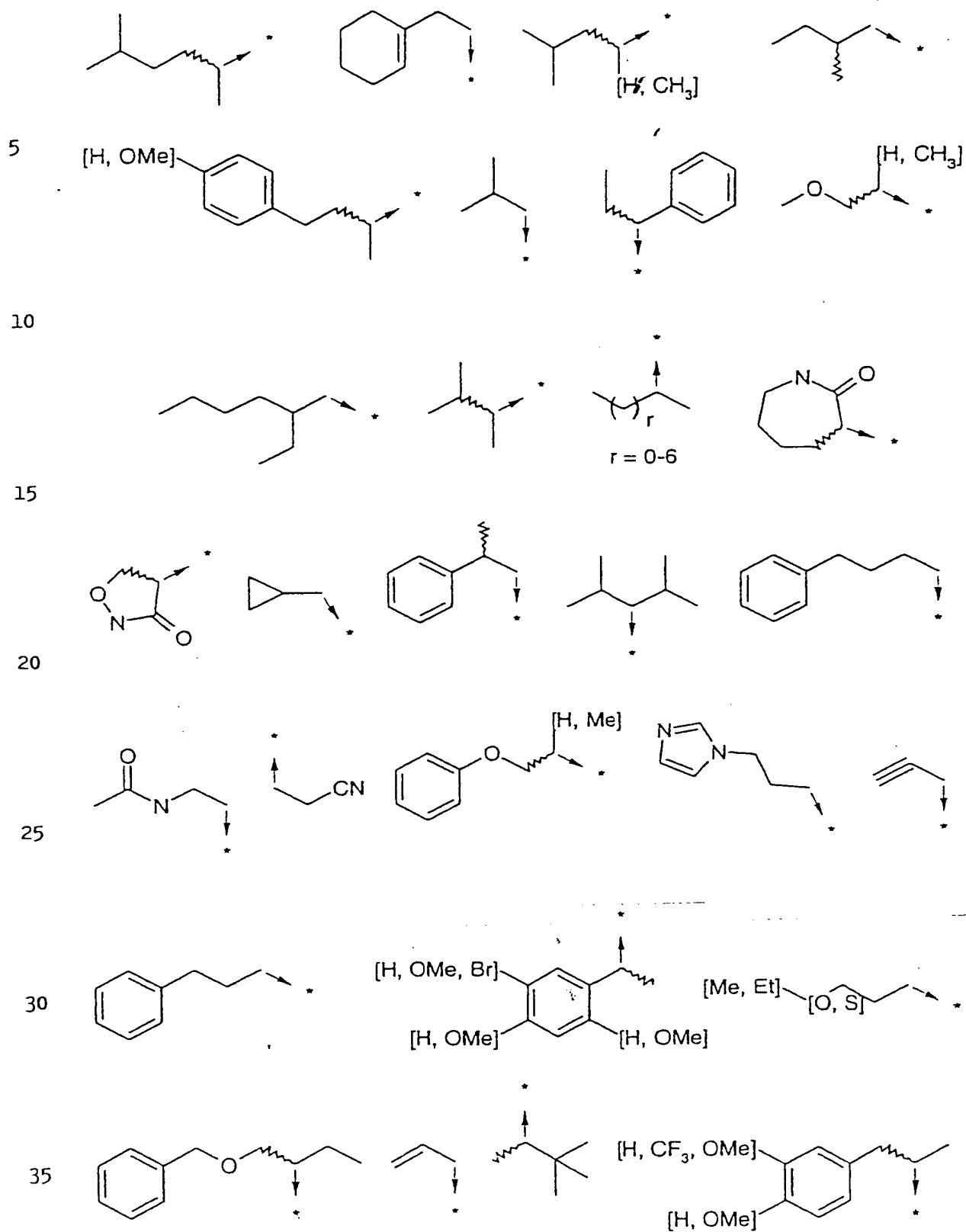
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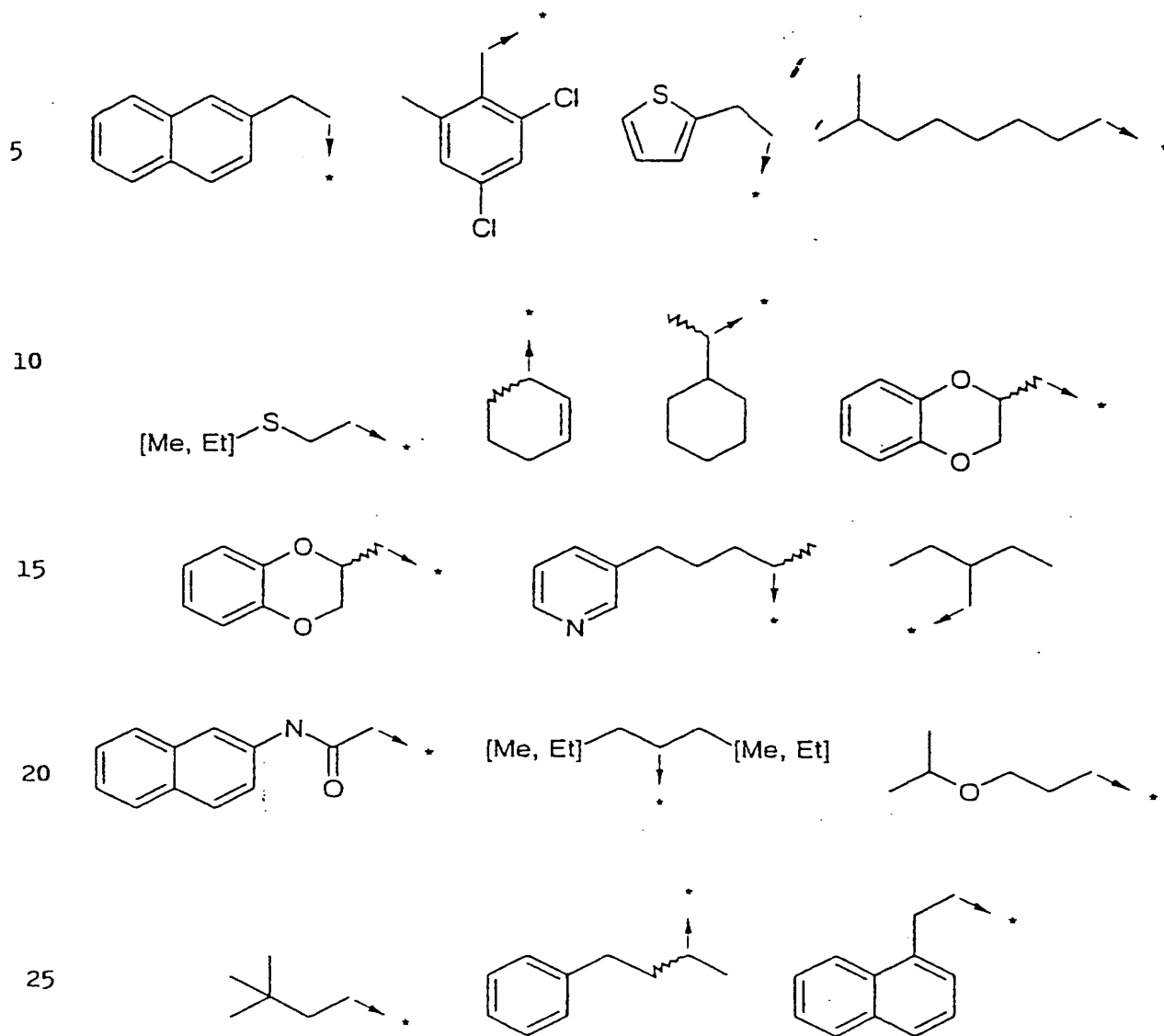


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- R2 groups already described in method A

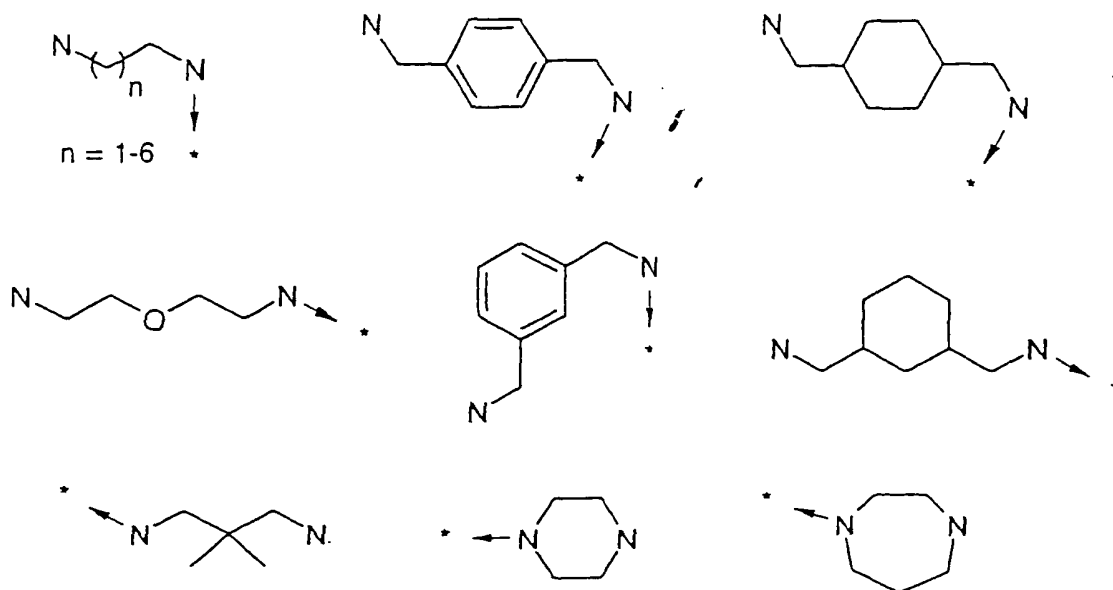
30 - R3 = -CO-R5

- R4 = H

- R5 groups:

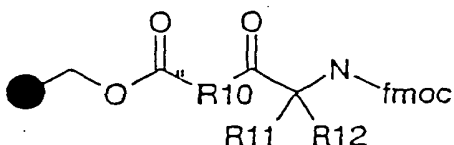
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#### METHOD F

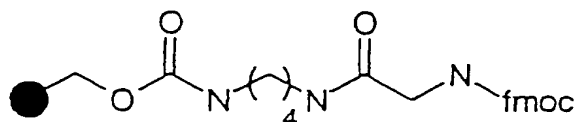
- 5 Preparation of monoprotected diamine resins functionalized with N-protected amino acids (Fmoc)



- 10 General procedure: the peptide coupling of the monoprotected diamine resins with N-Fmoc amino acids (4 to 10 eq.) which are commercially available (Bunin, B.A. *The Combinatorial Index*, Academic Press, 1998, p. 77-82) is carried out in DMF at ambient temperature for 1 to 24 hours with different standard coupling agents (4 to 10 eq.) such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), a DIC/N-hydroxybenzotriazole (HOBt) mixture, benzotriazolyloxytris(dimethylamino) phosphonium hexafluorophosphate (PyBOP), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) or 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU). The resin is then washed successively with DMF and DCM. The coupling sequence can be repeated (once or twice) until the Kaiser ninhydrin test is negative.
- 15

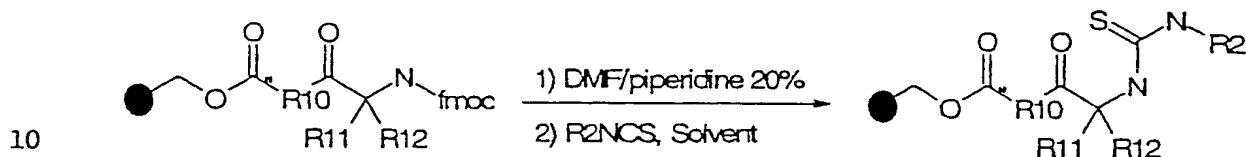
### Preparation 23

4-((((9H-fluoren-9-ylmethoxy)carbonyl)amino)acetyl)amino]butyl Wang resin - N-carbamate



5 Fmoc-Gly-OH acid (2.36 g, 7.94 mmol) is activated with HOBt (1.07 g, 7.94 mmol) and DIC (1.25 ml, 7.94 mmol) in 22 ml of DMF for 5 minutes before adding the mixture to butylamine Wang resin N-carbamate (1 g, load rate of 0.794 mmol/g) preswollen in 10 ml of DMF. After agitation for 18 hours at ambient temperature, the resin is washed successively with DMF (5 x 20 ml) then with DCM (5 x 20 ml) before being dried under vacuum. 1.27 g of pale yellow resin is thus obtained presenting a negative Kaiser ninhydrin test.

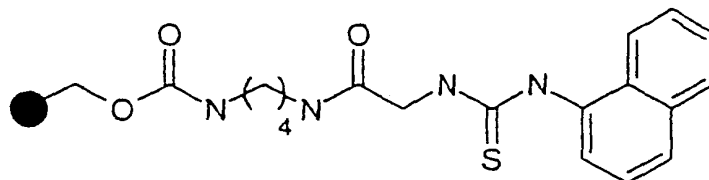
### Preparation of the thiourea resins



15 General procedure: a resin described above is deprotected with a 20% DMF/piperidine mixture. After agitation for one hour at ambient temperature, the resin is filtered and washed successively with DMF then with DCM. The deprotection/washing sequence is repeated a second time and the resin is dried under vacuum. The latter is preswollen in a solvent such as DMF or DCM then an aromatic or heteroaromatic isothiocyanate (5 to 10 eq.) is added. The mixture is agitated for 2 to 24 hours at ambient temperature before the resin is filtered and washed successively with DMF then with DCM. The resin is then dried under vacuum and a negative Kaiser ninhydrin test confirms that the substitution reaction is complete.

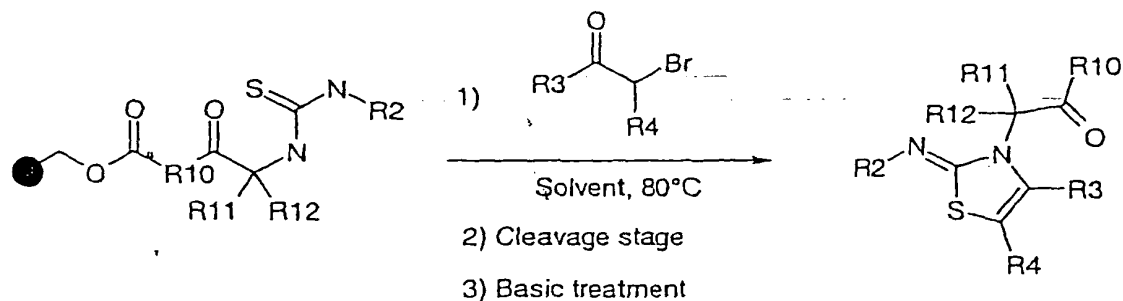
### Preparation 24

4-((((1-naphthylamino)carbothioyl)amino)acetyl)amino]butyl Wang resin *N*-carbamate



1.27 g of the above resin (see Preparation 23) is deprotected with 14 ml of DMF/piperidine at 20%. The mixture is agitated for one hour at ambient temperature. The resin is then filtered then washed with DMF (5 x 30 ml) then with DCM (5 x 30 ml). The deprotection/washing sequence is repeated once before the resin is dried under vacuum. 0.781 g of pale yellow resin was thus obtained with a load rate of 0.758 mmol/g calculated after elemental analysis of the sulphur. 416 mg (2.2 mmol, 10 eq.) of 1-naphthylisothiocyanate diluted in 6 ml of DMF is added to 0.3 g (0.22 mmol) of this thiourea resin. The mixture is agitated for 18 hours at ambient temperature. The resin is filtered then washed successively with DMF (5 x 20 ml) then with DCM (5 x 20 ml). 310 mg of a pale yellow resin is isolated after drying under vacuum with a load rate of 0.66 mmol/g calculated after elemental analysis of the nitrogen.

### Synthesis of 2-arylimino-2,3-dihydrothiazoles

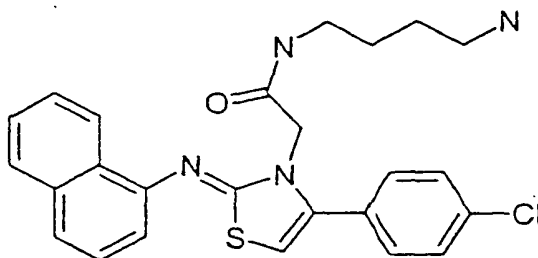


General procedure: the regioselective cyclization stage is carried out in aprotic solvents such as dioxane, DMF or *N*-methylpyrrolidinone at 80 °C for 2 to 3 hours between the thiourea resin and the  $\alpha$ -bromoketone (2 to 5 eq.). The resin is then washed successively with DMF, methanol and DCM then dried under reduced pressure. The 2-arylimino-2,3-dihydrothiazole resin is cleaved under acid conditions (DCM/trifluoroacetic acid at 50%) for 1 to 2 hours then rinsed with DCM. The solvent

is evaporated off and the free base isolated after treatment under basic conditions (saturated solution of sodium hydrogen carbonate) followed by an extraction with DCM or elution with methanol in a basic alumina cartridge (500 mg, Interchim).

### Example 6

- 5 *N*-(4-aminobutyl)-2-((2*Z*)-4-(4-chlorophenyl)-2-(1-naphthylimino)-1,3-thiazol-3(2*H*)-yl)acetamide  
(C<sub>25</sub>H<sub>25</sub>ClN<sub>4</sub>OS, MM = 465.02):

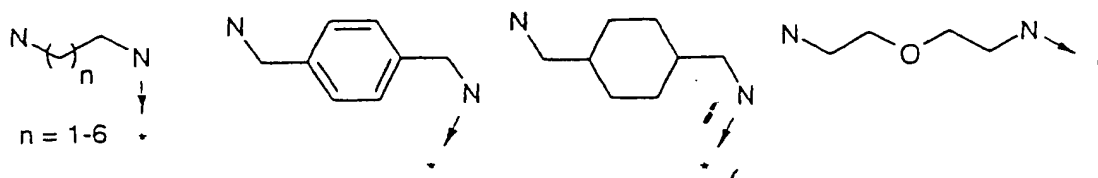


- 10 80 mg (52.8  $\mu$ mol, load rate of 0.66 mmol/g) of thiourea resin (Preparation 24) and 25.1 mg (105.6 mmol, 2 eq.) of 2-bromo-4'-chloroacetophenone are diluted in 1 ml of DMF. The mixture is heated at 80°C for 2 hours. The resin is filtered then washed with DMF (5 x 1 ml), methanol (5 x 1 ml) then DCM (5 x 1 ml) before being dried under vacuum. 1 ml of a 50% DCM/TFA mixture is added followed by agitation for 1 hour 30 minutes. The resin is filtered and rinsed with DCM. The filtrate is evaporated then rediluted in  
15 methanol for elution on basic alumina. 20.6 mg (yield of 84%; UV purity of 94.2 % at 220 nm) of yellow solid is thus isolated after evaporation corresponding to the free base.

- 20 NMR <sup>1</sup>H (DMSO D<sub>6</sub>, 100 MHz,  $\delta$ ): 8.36 (t, 1H, J = 4.7 Hz, NH); 8.12 (dd, 1H, J = 2.1 and 7.3 Hz); 7.87 (dd, 1H, J = 2.7 and 6.3 Hz); 7.63-7.34 (m, 8H); 7.13 (dd, 1H, J = 1.6 and 6.7 Hz); 6.33 (s, 1H, H azole); 4.44 (broad s, 2H); 3.14 (m, 2H); 2.7 (m, 2H); 1.5 (m, 4H). MS/LC: m/z = 465.21 (M+H)<sup>+</sup>.

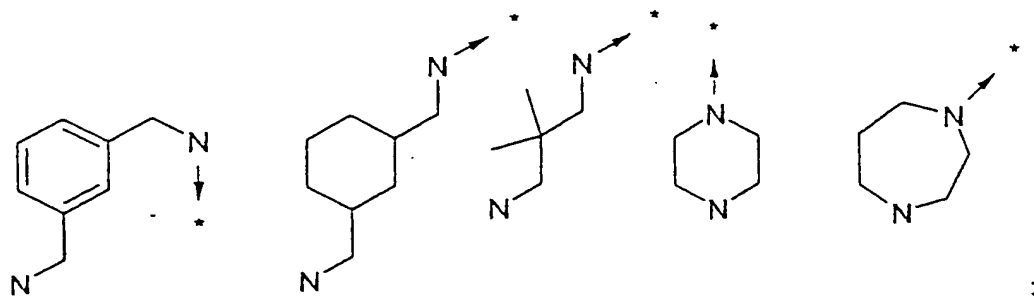
A series of 2-arylimino-2,3-dihydrothiazoles was synthesized according to method F using our robotic system (ACT MOS 496):

- 25 - R1 = -C(R11R12)-CO-R10  
- R2, R3 and R4 groups already described in method A  
- R10 groups:



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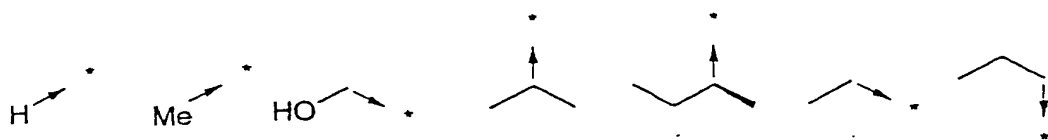


- R11 = H

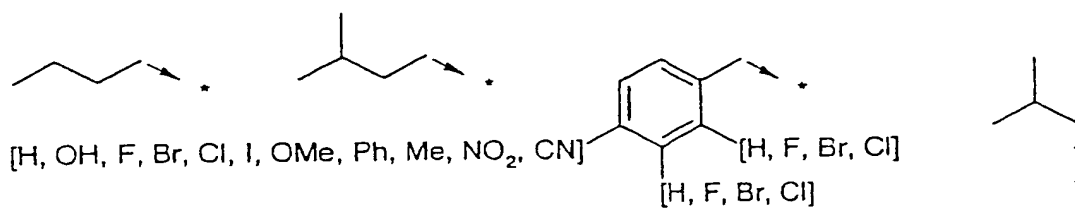
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- R12 groups:

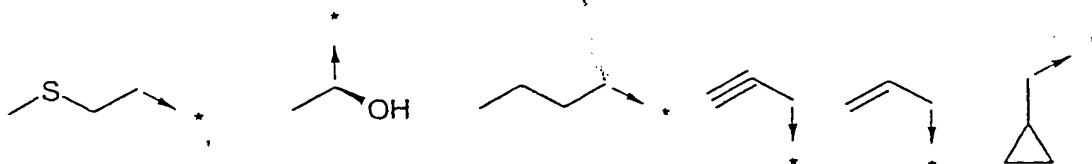
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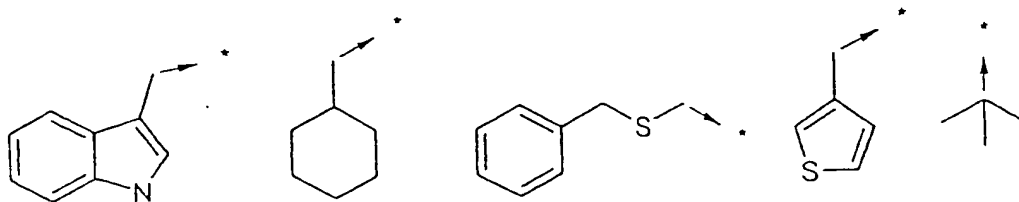
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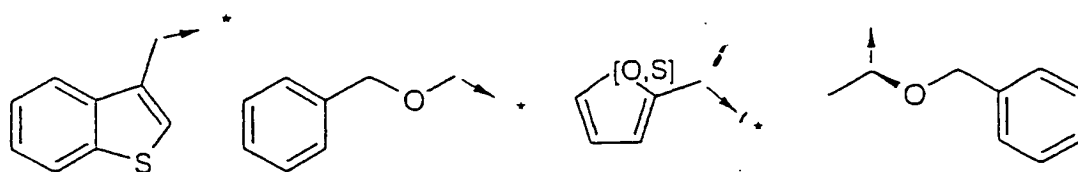
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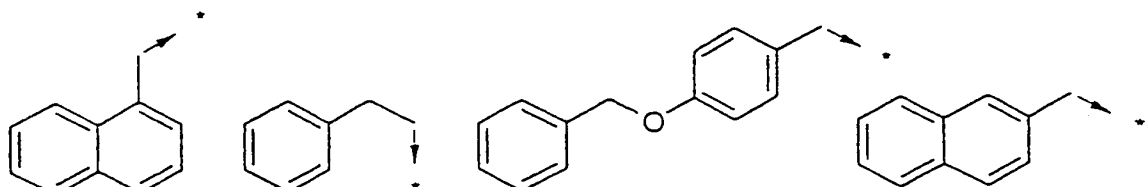
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## EXAMPLES

Examples obtained according to methods A, B, C, D, E and F described above are shown below in the tables. These examples are shown to illustrate the above processes and must not in any circumstances be considered as limiting the scope of the invention.

- 5 The compounds obtained have been characterized by their retention times (rt) and by mass spectrometry (M+H)<sup>+</sup>.

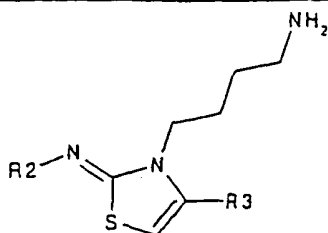
The chromatograms are obtained from a high performance liquid chromatography device (Hewlett-Packard 1100) equipped with a scanning UV detector. The following conditions were used to measure the retention times by high performance liquid chromatography, it being understood that the extraction wavelength of each of the chromatograms is 220 nm:

t (min.)	A (%)	B (%)
0	90	10
6	15	85
8	15	85

Eluent A: water + 0.02% trifluoroacetic acid; eluent B: acetonitrile.

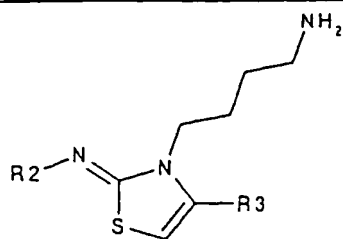
Flow rate: 1 ml/min; volume injected: 5  $\mu$ l; temperature: 40 °C. Column: Uptisphere 3 $\mu$ m ODS, 50 x 4.6 mm i.d. (Interchim)

- 15 The mass spectra are obtained from a single quadrupole mass spectrometer equipped with an *electrospray* source (Micromass, Platform II).

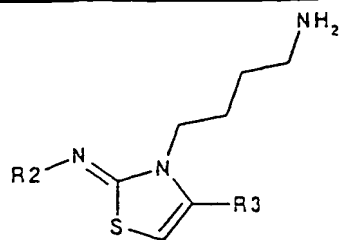


Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
7			91.2	3.09	304.2
8			93.1	3.38	338.2
9			94	3.56	352.2
10			93.3	3.42	338.2
11			96.6	3.25	342.2
12			96.4	3.46	365.2
13			91.9	3.86	393.2
14			96.4	3.44	358.2
15			95.6	3.34	382.2
16			94.5	3.7	408
17			54.43	2.9	305.2
18			50.4	3.14	339.2





Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
19			48.9	3.38	535.2
20			39.3	3.26	339.2
21			49.5	3.06	343.2
22			42.3	3.29	366.2
23			43.4	3.7	394.3
24			56.7	3.16	359.2
25			45.3	3.09	383.2
26			45.7	3.3	409
27			96.8	3.41	332.3
28			92.8	3.7	366.3
29			90.6	3.84	380.3
30			93.7	3.76	366.3



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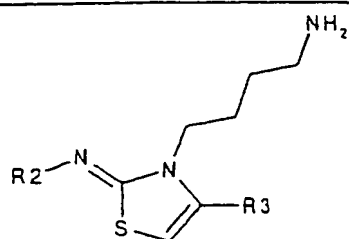
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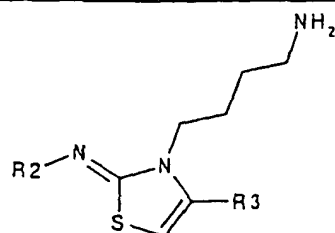
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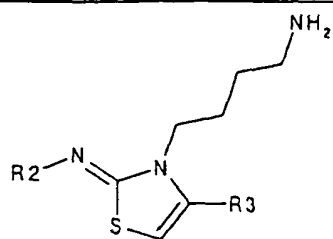
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
31			94.4	3.63	370.2
32			89.1	3.82	393.2
33			90.1	4.12	410.2
34			96.7	3.83	386.2
35			95.8	3.67	410.2
36			93.4	4.17	436.1
37			88.4	3.64	329.25
38			91.8	4.03	363.2
39			88.6	4.15	377.2
40			94.1	4.22	363.2
41			95.2	4.1	376.2
42			92.8	4.35	390.2



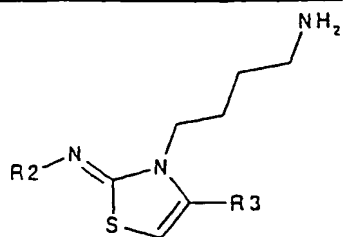
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
43			94.1	4.54	418.2
44			95	4.34	383.1
45			95.1	4.06	407.2
46			93	4.7	433.1
47			96.4	3.32	332.3
48			92.9	3.62	366.3
49			95.6	3.76	380.3
50			95.6	3.64	366.33
51			96	3.51	370.2
52			87	3.69	390.2
53			80.9	4.04	421.3
54			97.1	3.7	436.1



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
55			94.6	3.59	410.2
56			95.6	3.92	436.1
57			82.1	3.66	368.2
58			90.7	3.94	402.2
59			85.5	4.06	416.2
60			94.4	4.09	402.2
61			95.1	3.99	406.2
62			93.6	4.21	429.2
63			93.6	4.39	457.2
64			96	4.22	422.1
65			91.6	3.96	446.2
66			94.5	4.65	472



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
67			97	3.07	348.2
68			93.6	3.36	382.2
69			93.4	3.54	396.2
70			94.7	3.41	382.1
71			96.3	3.24	386.2
72			94.5	3.44	409.1
73			93.4	3.83	437.2
74			95.4	3.41	402.1
75			95.7	3.32	426.2
76			92.4	3.64	452.2
77			98.1	3.66	324.2
78			91.2	3.98	388.2



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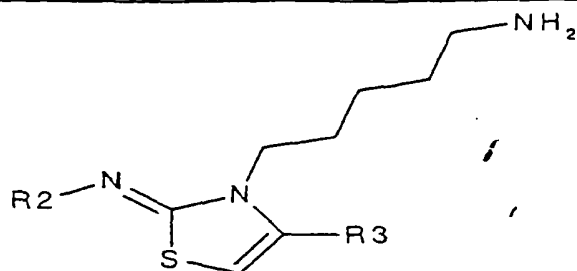
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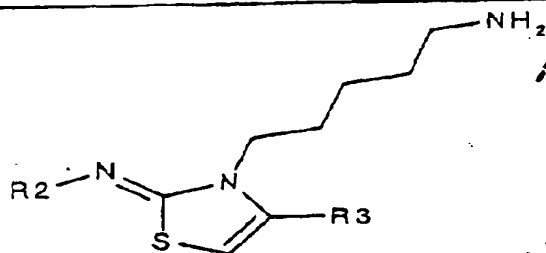
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
79			81.9	4.09	402.2
80			96.1	4.12	388.2
81			96.1	4.03	392.2
82			94.2	4.24	415.2
83			93.3	4.39	443.3
84			96.3	4.28	408.1
85			94.2	4.0	432.2
86			95.6	4.7	458.1



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
87			97	3.35	338.2
88			94	3.51	352.3
89			94	3.58	352.3
90			97	3.42	356.2
91			86	4.01	422.2
92			96	3.99	407.3
93			7	3.65	391.3
94			92	4.11	378.2
95			95	3.43	435.2
96			97	3.91	422.1
97			43	3.19	339.2
98			32	3.33	353.2



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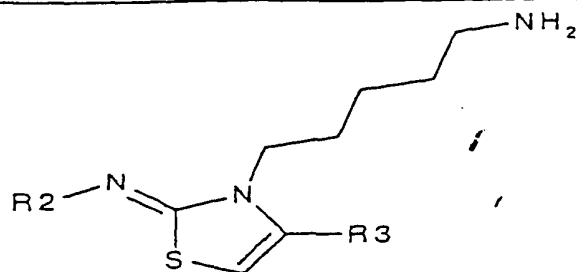
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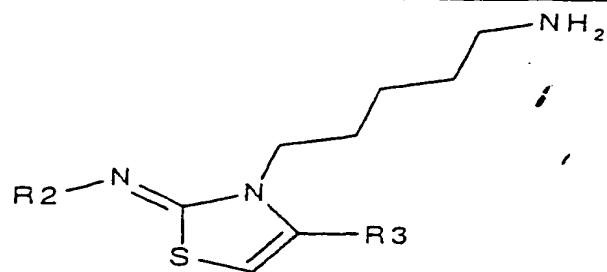
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
99			39	3.45	353.2
100			39	3.28	357.2
101			42	3.8	423.2
102			41	3.89	408.2
103			14	3.43	392.2
104			39	3.62	379.2
105			28	3.2	436.2
106			35	3.56	423.1
107			95	4.65	464.1
108			89	4.64	478.2
109			82	4.88	478.1
110			92	4.76	482.1

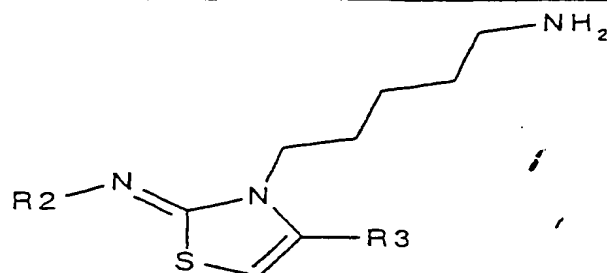




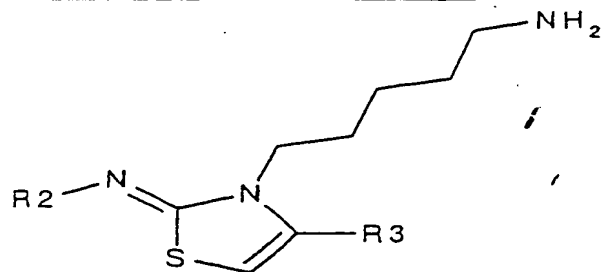
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
111			90	5.41	548.1
112			86	5.13	533.2
113			9	4.5	517.1
114			95	5.49	504.1
115			80	4.4	561.1
116			89	5.4	548.0
117			96	4.85	422.2
118			91	4.86	436.2
119			88	5.08	436.2
120			95	4.96	440.2
121			81	5.56	506.2
122			83	5.34	491.2



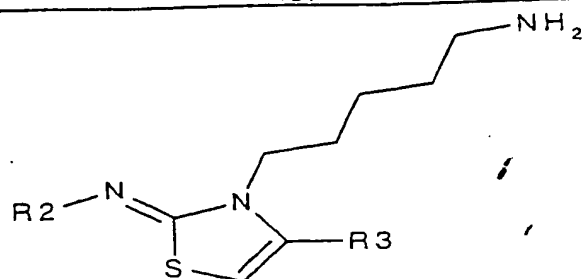
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
123			3	4.7	475.3
124			91	5.59	462.2
125			92	4.61	519.2
126			92	5.52	506.1
127			98	3.63	366.3
128			97	3.76	380.3
129			98	3.82	380.3
130			98	3.67	384.2
131			97	4.16	450.2
132			96	4.2	435.3
133			21	3.9	419.3
134			88	4.28	406.2



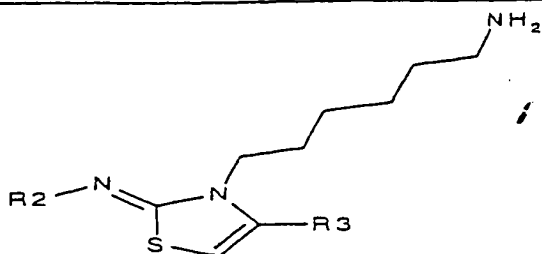
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
135			97	3.68	463.3
136			82	4.09	450.1
137			93	3.44	417.2
138			94	3.5	431.2
139			95	3.71	431.2
140			95	3.58	435.2
141			94	4.27	501.2
142			93	4.05	486.6
143			94	4.28	457.2
144			92	3.39	514.2
145			85	4.16	501.1
146			97	3.36	382.2



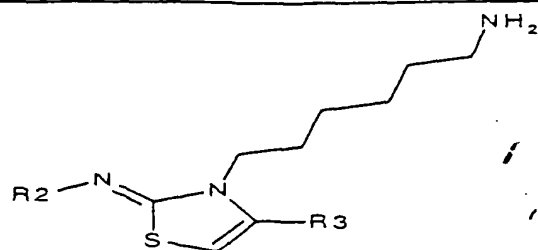
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
147			94	3.53	396.2
148			97	3.6	396.2
149			97	3.43	400.2
150			97	3.95	466.2
151			95	4.01	451.3
152			15	3.57	435.2
153			94	4.0	422.2
154			95	3.45	479.3
155			95	3.84	466.1
156			96	4.11	388.2
157			90	4.14	402.2
158			96	4.31	402.2



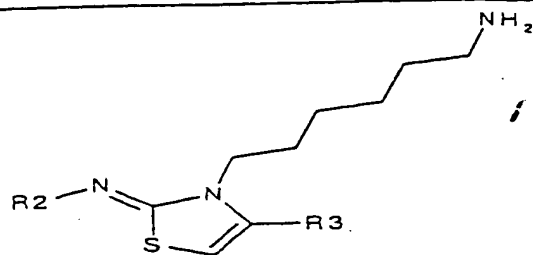
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
159			96	4.21	406.2
160			97	4.83	472.3
161			95	4.57	457.3
162			96	5.12	428.2
163			88	4.01	485.3
164			97	4.91	472.1



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
165			93	3.52	332.3
166			99	3.76	370.3
167			97	3.9	393.3
168			98	4.25	436.2
169			98	4.14	431.2
170			99	4.79	488.2
171			98	3.74	410.2
172			98	4.28	410.3
173			98	4.38	392.2
174			98	4.73	456.2
175			98	4.06	374.3
176			98	4.37	412.3

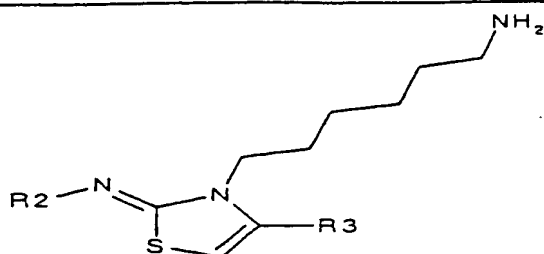


Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
177			97	4.46	435.3
178			98	4.8	478.3
179			99	4.78	473.3
180			94	5.43	530.3
181			97	4.27	452.3
182			85	4.73	452.4
183			98	5.07	434.3
184			93	5.33	498.3
185			98	4.61	458.2
186			97	5.23	496.1
187			96	5.34	519.1
188			97	5.72	562.1

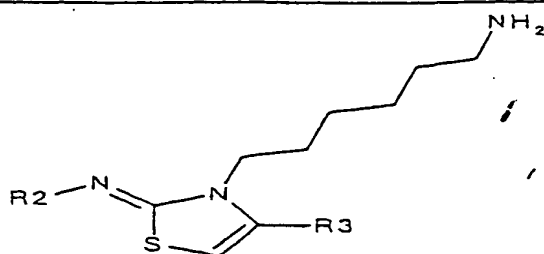


Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
189			98	5.57	557.1
190			96	6.16	614.1
191			96	4.97	536.1
192			85	5.67	536.2
193			96	5.86	518.1
194			97	6.32	582.1
195			96	4.16	357.3
196			98	4.74	395.2
197			97	4.86	418.2
198			98	5.26	461.2
199			98	5.12	456.2
200			97	5.72	513.2

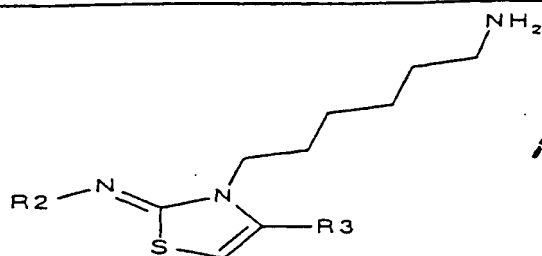




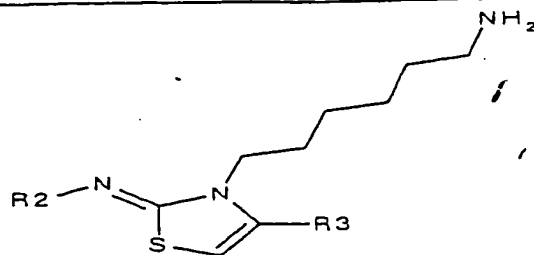
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
201			96	4.51	435.2
202			98	5.18	435.3
203			95	5.37	417.2
204			95	5.84	481.2
205			96	3.63	350.3
206			98	3.95	388.2
207			95	4.07	411.2
208			98	4.44	454.2
209			97	4.38	449.2
210			89	5.03	506.2
211			96	3.87	428.2
212			97	4.4	428.3



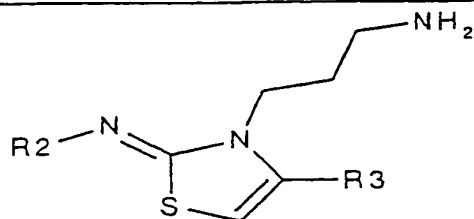
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
213			96	4.63	410.2
214			96	4.96	474.2
215			94	5.38	411.2
216			98	5.63	449.2
217			96	5.77	472.2
218			98	6.04	515.2
219			98	5.74	510.1
220			91	6.29	567.2
221			98	5.53	489.2
222			96	6.38	489.3
223			97	6.0	471.2
224			98	6.49	535.1



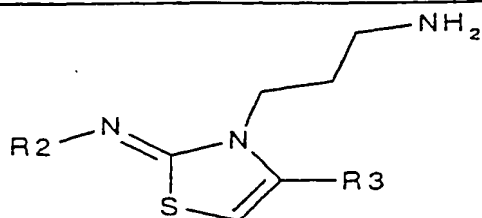
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
225			98	3.99	426.3
226			98	4.34	464.2
227			96	4.43	487.3
228			97	4.78	530.2
229			98	4.76	525.2
230			96	5.36	582.2
231			95	4.23	504.3
232			97	4.7	504.3
233			98	4.99	486.2
234			97	5.3	550.2
235			96	3.44	411.2
236			95	3.94	449.2



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
237			96	4.11	472.3
238			95	4.52	515.2
239			95	4.39	510.2
240			94	5.01	567.2
241			96	3.74	489.2
242			96	4.41	489.3
243			96	4.56	471.2
244			97	5.01	535.2



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
245			98.1	3.2	290.2
246			96.9	3.78	324.2
247			69.3	3.88	355.2
248			99.3	3.79	335.2
249			99.4	3.86	324.2
250			98	3.97	351.2
251			98.7	4.14	388.1
252			93.5	4.24	379.3
253			82.4	5.16	446.2
254			98.8	3.7	368.2
255			98.5	3.9	332.3
256			92.3	4.4	366.3



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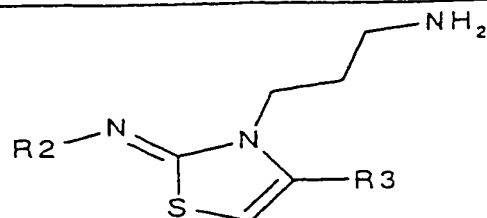
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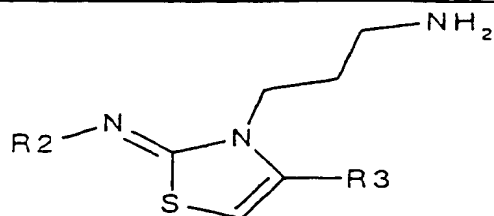
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
257			82.3	4.55	397.2
258			98.4	4.48	377.3
259			97.3	4.49	366.3
260			95.4	4.59	393.3
261			98.7	4.77	430.2
262			90.9	4.76	421.3
263			98.7	5.72	488.2
264			97.7	4.33	410.3
265			98.5	3.42	369.2
266			94.9	3.91	403.2
267			98.1	3.81	434.2
268			97.9	3.78	414.1

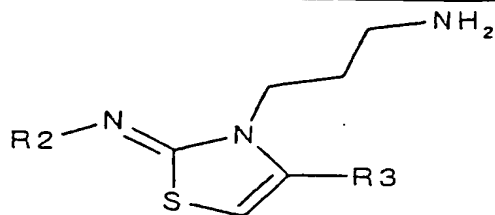


Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
269			98.1	4.06	403.2
270			96.2	4.14	430.2
271			98.3	4.28	467.1
272			96.8	4.5	458.2
273			98.3	4.92	525.2
274			97.1	3.84	447.2
275			96.5	4.28	354.2
276			93.3	5.02	388.2
277			68.7	4.96	419.2
278			97.8	4.86	399.2
279			96	5.13	388.2
280			96.9	5.18	415.2

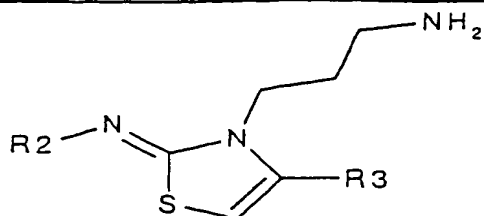


Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
281			98.6	5.31	452.1
282			89.5	5.54	443.2
283			65.5	5.89	510.2
284			97.8	4.89	432.2
285			93.2	5.08	369.2
286			94.6	5.31	403.1
287			97.6	5.07	434.1
288			99.1	5.05	414.1
289			99.1	5.39	403.1
290			98.3	5.44	430.2
291			99.4	5.47	467.1
292			97.4	5.86	458.2

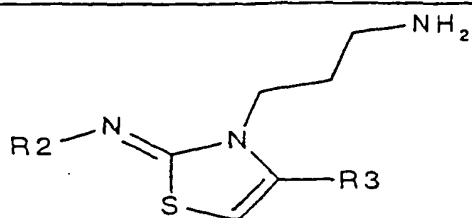




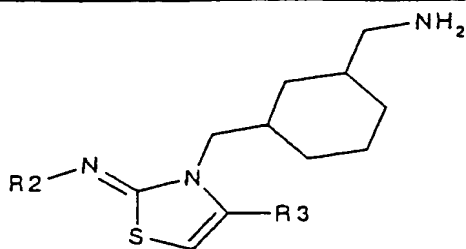
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
293			99.5	5.87	525.1
294			98.5	5.21	447.2
295			95.7	4.41	396.3
296			92.9	5.06	430.3
297			54	5.19	461.2
298			91.8	5.07	441.2
299			95.8	5.18	430.3
300			96	5.28	457.3
301			96.9	5.45	494.2
302			87	5.49	485.3
303			35.6	6.18	552.2
304			96.7	4.97	474.3



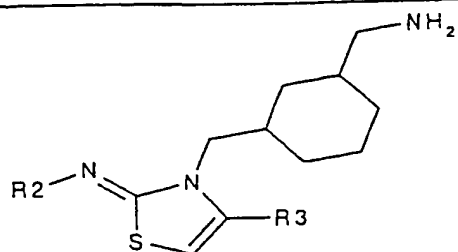
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
305			83.9	5.24	380.2
306			92.8	5.39	414.2
307			92	5.14	445.2
308			97.4	5.11	425.1
309			98.1	5.47	414.2
310			97.2	5.47	441.1
311			97	5.52	478.1
312			93.3	5.99	469.2
313			98.3	5.91	536.1
314			96.5	5.31	458.2
315			98.7	4.12	340.3
316			93.4	4.66	374.2



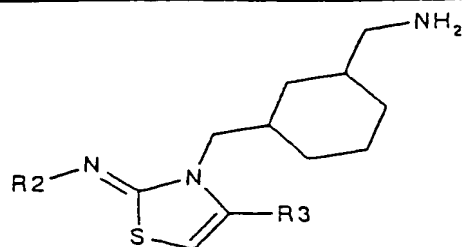
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
317			98.9	4.78	405.2
318			97.8	4.71	385.2
319			98.1	4.78	374.2
320			97.2	4.9	401.2
321			98.8	5.09	438.1
322			95.8	5.07	429.3
323			98.5	5.82	496.2
324			97.5	4.59	418.2



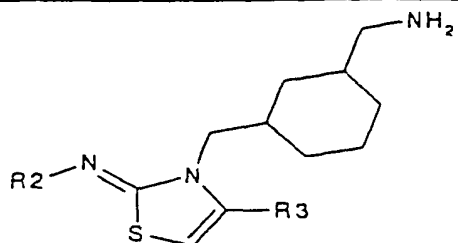
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
325			93	3.71	358.2
326			68 + 30	4.0 + 4.1	396.2
327			69 + 31	4.5 + 4.6	462.2
328			66 + 27	4.7 + 4.8	484.3
329			67 + 31	4.4 + 4.6	457.2
330			67 + 30	4.3 + 4.5	541.2
331			62 + 33	3.9 + 4.0	436.2
332			64 + 30	3.5 + 3.6	447.3
333			65 + 30	4.7 + 4.9	418.2
334			68 + 29	3.8 + 3.9	372.3
335			69 + 29	4.2 + 4.3	410.2
336			68 + 30	4.6 + 4.8	476.2



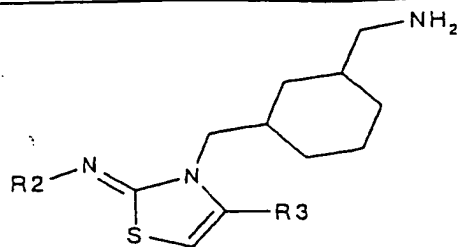
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
337			61 + 32	4.8 + 4.89	498.3
338			66 + 30	4.55 + 4.71	471.2
339			68 + 29	4.46 + 4.58	555.2
340			22 + 11	5.13 + 5.22	520.4
341			67 + 24	4.09 + 4.14	450.3
342			71 + 23	3.7 + 3.74	461.3
343			67 + 31	4.82 + 5.02	432.2
344			66 + 31	4.14 + 4.39	404.3
345			65 + 31	4.74 + 4.94	442.2
346			65 + 31	5.25 + 5.47	508.2
347			62 + 29	5.28 + 5.5	530.3
348			65 + 30	5.21 + 5.38	503.2



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
349			63 + 30	5.03 + 5.24	587.2
350			64 + 30	5.59 + 5.84	552.3
351			58 + 28	4.49 + 4.66	482.3
352			64 + 26	4.01 + 4.11	493.3
353			65 + 31	5.54 + 5.71	464.2
354			57 + 24	4.08 + 4.19	399.3
355			62 + 28	4.52 + 4.7	437.2
356			62 + 28	5 + 5.2	503.2
357			58 + 26	5.08 + 5.25	525.3
358			62 + 29	4.98 + 5.19	498.2
359			62 + 29	4.82 + 4.99	582.2
360			62 + 28	5.39 + 5.58	547.3

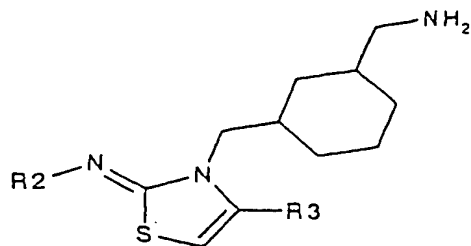


Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
361			56 + 26	4.37 + 4.49	477.3
362			64 + 32	5.32 + 5.55	459.2
363			94	6.36	505.2
364			98	6.39	542.1
365			25 + 72	6.74 + 6.77	608.1
366			92	7.07	630.2
367			23 + 73	6.38 + 6.42	603.1
368			26 + 69	6.73 + 6.76	687.1
369			60	7.55	652.3
370			82	6.39	582.1
371			94	5.74	593.2
372			22 + 73	6.68 + 6.74	564.1

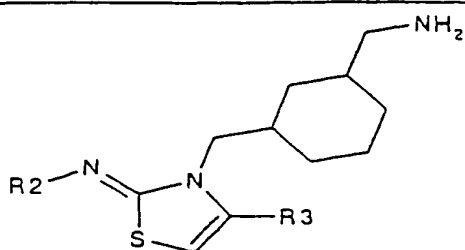


Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
373			59 + 27	4.88 + 5.13	403.3
374			67 + 30	5.35 + 5.44	441.2
375			64 + 34	5.84 + 5.92	507.2
376			62 + 28	6 + 6.13	529.3
377			97	5.58	502.2
378			65 + 32	5.71 + 5.8	586.2
379			49 + 23	6.45 + 6.58	551.3
380			61 + 26	5.18 + 5.3	481.2
381			45 + 21	4.57 + 4.68	492.3
382			84	5.9	463.2
383			56 + 26	4.65 + 4.89	410.2
384			64 + 30	5.29 + 5.47	448.2

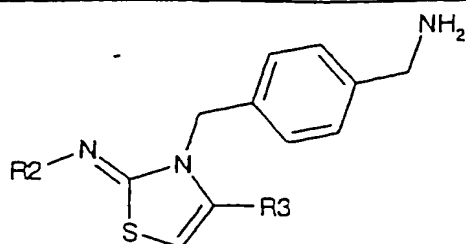




Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
385			65 + 30	5.78 + 5.95	514.2
386			63 + 27	5.8 + 6.02	536.2
387			65 + 31	5.71 + 5.81	509.1
388			62 + 32	5.59 + 5.79	593.1
389			30 + 14	6.22 + 6.45	558.3
390			57 + 26	5.01 + 5.2	488.2
391			54 + 26	4.46 + 4.61	499.2
392			27 + 11	6.09 + 6.18	470.2
393			63 + 29	4.53 + 4.6	464.3
394			65 + 30	4.78 + 4.93	502.3
395			61 + 28	5.16 + 5.35	568.2
396			59 + 25	5.3 + 5.42	590.3



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
397			60 + 30	5.12 + 5.34	563.2
398			63 + 32	5.01 + 5.17	647.2
399			59 + 26	5.55 + 5.7	612.4
400			52 + 14	4.35 + 4.4	553.3
401			61 + 29	5.36 + 5.64	524.3



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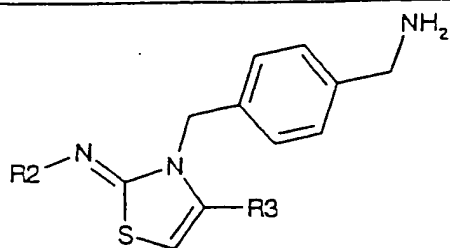
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
402			88.5	4.52	442.1
403			94.6	4.72	432.15
404			95	4.78	455.16
405			98.6	5.19	493.12
406			95.8	4.99	577.11
407			95.1	4.44	472.19
408			96.3	4.0	483.21
409			94.5	5.35	498.04
410			94.1	5.61	454.15
411			83	5.43	526.03
412			94.9	5.4	515.97
413			93.4	5.52	539.00



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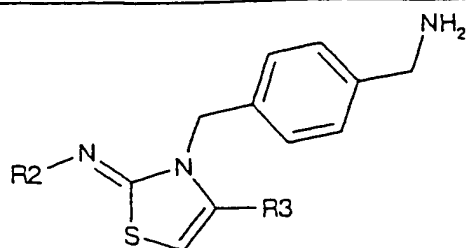
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
414			97.1	5.48	576.95
415			92.7	5.69	660.99
416			92.2	5.27	555.98
417			92	4.7	567.00
418			89.7	5.73	581.87
419			87.8	5.77	538.00
420			84.4	4.74	446.14
421			92.6	4.9	436.08
422			91.2	5.0	459.10
423			72.4	5.0	487.16
424			94.9	5.19	497.07
425			91.7	5.18	581.05



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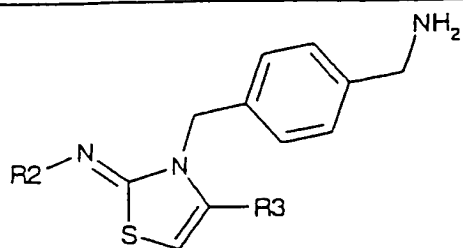
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
426			91.5	4.67	476.12
427			89.6	4.16	487.13
428			91.7	5.38	501.96
429			89.9	5.48	458.10
430			87.1	5.26	484.14
431			95.7	5.41	474.10
432			94.6	5.51	497.12
433			97.4	5.64	535.01
434			96.2	5.69	619.04
435			94.4	5.21	514.10
436			94.7	4.67	525.11
437			92.7	5.84	539.94



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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
438			91	5.93	496.09
439			82.4	4.82	492.18
440			92.2	5.03	482.14
441			90.4	5.08	505.15
442			33.4	5.14	533.18
443			97.6	5.45	543.07
444			93.9	5.26	627.10
445			93.6	4.78	522.14
446			94	4.34	533.15
447			91.6	5.6	547.98
448			92.6	5.82	504.14
449			84.9	5.76	468.08

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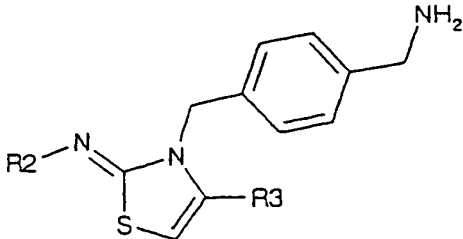
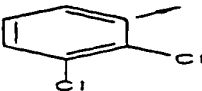
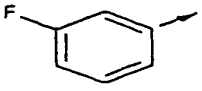
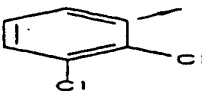
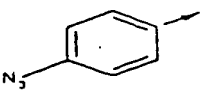

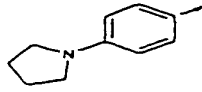
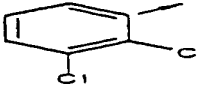
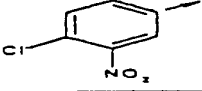
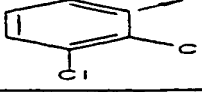
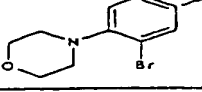
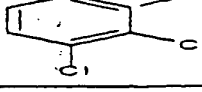
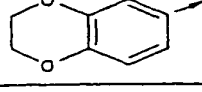
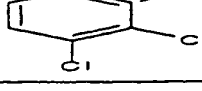
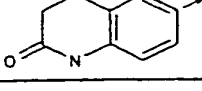
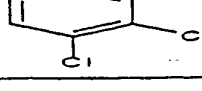
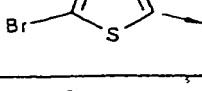
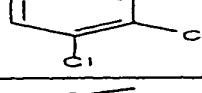
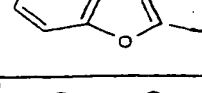
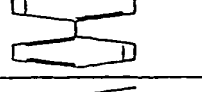


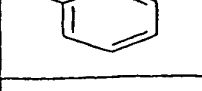

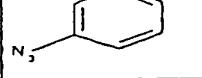
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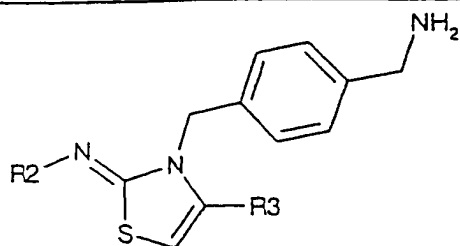
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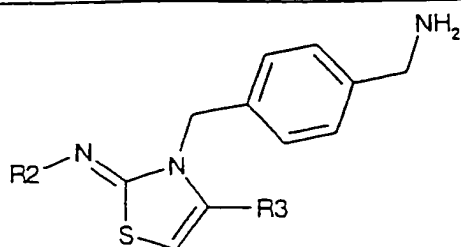
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
450			95.4	5.54	458.03
451			93.3	5.74	481.03
452			85.3	6.21	509.06
453			97.4	5.62	518.97
454			92	5.91	602.90
455			91.4	5.54	498.06
456			91.4	4.98	509.06
457			88.7	5.9	523.88
458			88.5	5.88	480.05
459			88.2	4.69	506.18
460			93.1	4.87	496.15
461			91.2	4.92	519.15

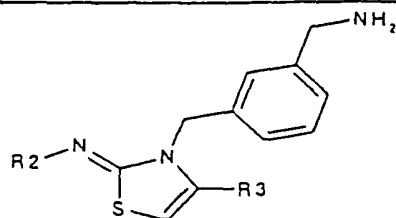


Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
462			26.9	5.01	547.17
463			93.9	5.26	557.08
464			93.2	5.08	641.13
465			95.7	4.64	536.15
466			95.3	4.24	547.15
467			92.3	5.39	562.00
468			92	5.6	518.14
469			75.3	4.59	494.13
470			97.1	4.73	484.11
471			95.4	4.81	507.11
472			10.7	4.9	535.14
473			96.4	5.07	545.02





Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
474			96.5	4.98	629.05
475			95.2	4.5	524.08
476			96	4.06	535.09
477			95.3	5.22	549.95
478			94.1	5.36	506.08



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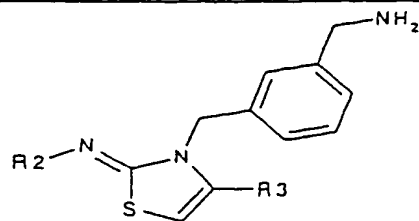
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
479			45.6	4.95	377.14
480			79	5.17	431.07
481			56.8	4.84	442.08
482			79.2	5.04	415.07
483			78.4	5.25	438.11
484			82.6	5.47	481.10
485			72.6	5.81	503.17
486			79	5.36	560.04
487			72.1	5.34	480.98
488			76.9	5.0	441.09
489			94.5	4.6	386.09
490			95.4	5.34	440.04



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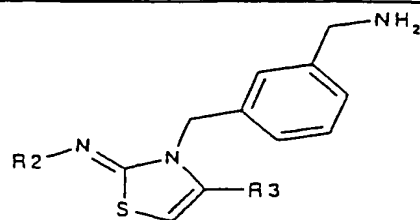
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
491			95.3	5.05	451.06
492			95.2	5.23	424.07
493			93.4	5.35	447.07
494			96.1	5.67	490.07
495			88.5	5.84	512.12
496			92.9	5.55	569.00
497			92.8	5.64	489.95
498			92	5.03	450.08
499			96.5	4.87	397.11
500			96.1	5.26	451.06
501			96.1	4.95	462.07
502			96.3	5.15	435.08



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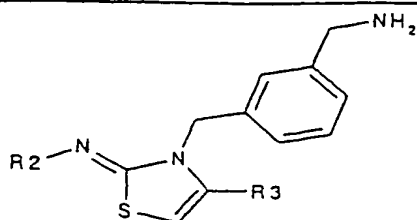
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
503			96.2	5.31	458.11
504			96.5	5.57	501.08
505			89.3	5.86	523.15
506			95.8	5.46	580.03
507			94.2	5.45	500.96
508			93.5	5.07	461.08
509			98.5	4.29	408.18
510			97.2	4.98	462.13
511			96.4	4.81	473.19
512			96.3	4.9	446.17
513			94.7	4.93	469.19
514			96.9	5.29	512.17



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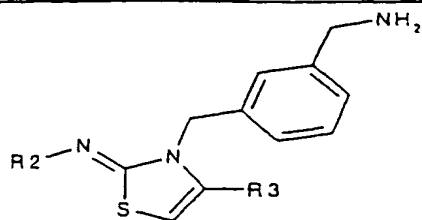
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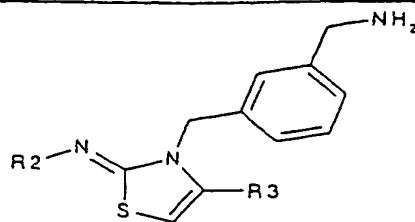
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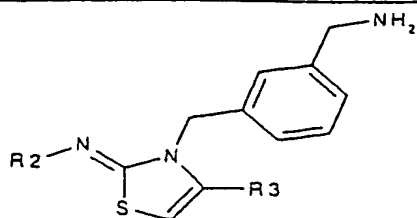
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
515			90.6	5.33	534.20
516			96.3	5.15	591.13
517			93.5	5.47	512.04
518			95	4.65	472.19
519			95.5	5.14	420.13
520			95.6	5.63	474.07
521			93.8	5.35	485.10
522			95.1	5.53	458.09
523			94.2	5.67	481.10
524			94.6	5.9	524.09
525			88.4	6.15	546.11
526			92.6	5.83	603.07



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
527			89.8	5.87	523.97
528			92.3	5.41	484.11
529			98.2	3.75	380.18
530			96.4	4.35	434.11
531			96.5	4.19	445.13
532			95.7	4.25	418.14
533			94.4	4.33	441.13
534			95.5	4.69	484.14
535			89.5	4.81	506.18
536			95.5	4.54	563.08
537			92.2	4.79	484.03
538			93.7	4.07	444.14

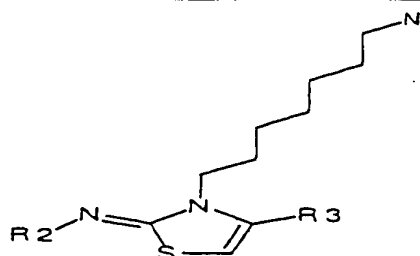


Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
539			95.4	4.25	416.10
540			95.7	5.05	470.07
541			95.6	4.81	481.05
542			95.4	4.96	454.07
543			94.4	5.05	477.10
544			95.9	5.4	520.04
545			89.5	5.51	542.11
546			94	5.26	599.02
547			92.9	5.4	519.93
548			92.3	4.72	480.08
549			92	6.01	585.84
550			96.7	6.18	639.79

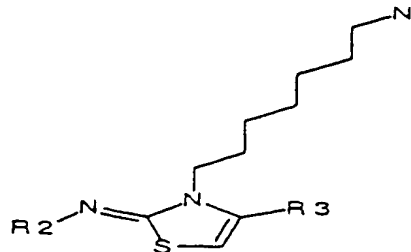


Ex.	R <sub>2</sub>	R <sub>3</sub>	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
551			95.8	5.84	650.83
552			96	6.04	623.81
553			94.7	6.22	646.85
554			95	6.39	689.82
555			88.8	6.7	711.88
556			94.9	6.4	768.76
557			95	6.35	689.71
558			93.7	6.01	649.83

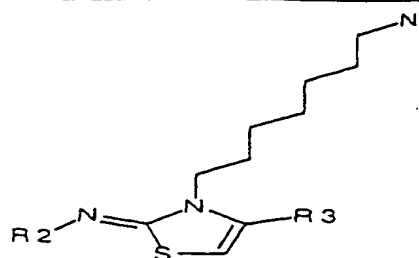




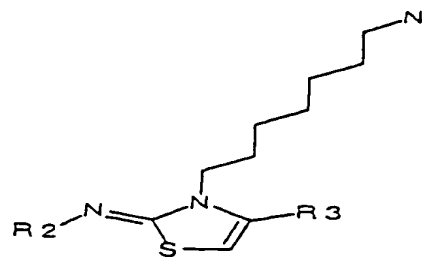
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
559			87.5	4.07	408.18
560			89.6	4.15	458.09
561			89.5	4.04	421.17
562			54.6	4.37	449.23
563			92.7	4.85	516.14
564			92.5	4.27	459.14
565			94.2	3.87	438.18
566			92.6	4.41	444.2
567			92.2	3.5	449.21
568			92.4	4.53	420.17
569			86.7	4.23	422.21
570			93.7	4.38	472.12



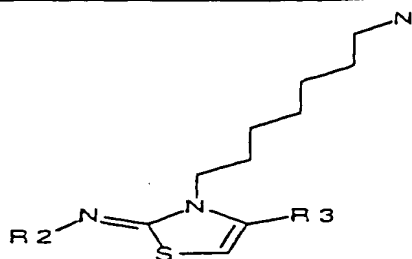
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
571			88.7	4.27	435.19
572			64.2	4.53	463.25
573			93.8	5.15	530.18
574			93.6	4.55	473.17
575			86.8	4.07	452.21
576			93.4	4.65	458.24
577			91.8	3.71	463.23
578			91.6	4.85	434.20
579			83.1	4.38	436.23
580			92.7	4.56	486.14
581			38.9	4.43	449.24
582			80.4	4.65	477.25



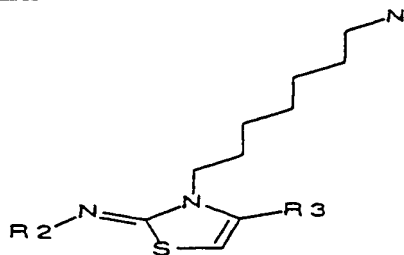
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
583			93	5.34	544.19
584			94.3	4.75	487.20
585			93.2	4.23	466.23
586			94	4.82	472.28
587			92.1	3.88	477.28
588			91.7	5.06	448.23
589			83.1	4.62	419.20
590			93	5.06	469.09
591			88	4.89	432.18
592			88.5	5.02	460.23
593			93.2	5.69	527.16
594			91.6	5.11	470.15



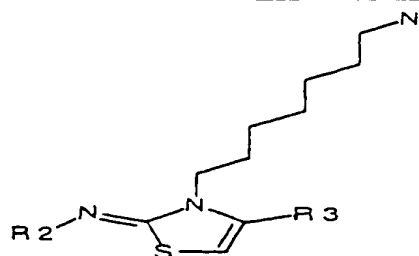
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
595			90.2	4.53	449.19
596			91.9	5.4	455.19
597			90.2	3.99	460.20
598			93	5.41	431.16
599			86.1	4.05	424.22
600			91.8	4.17	474.12
601			90.2	4.04	437.19
602			86.4	4.34	465.24
603			93.5	4.91	532.19
604			93.4	4.3	475.16
605			87.9	3.86	454.20
606			91.8	4.47	460.25



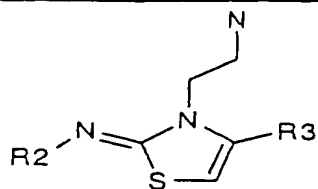
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
607			90.7	3.48	465.21
608			92	4.55	436.19
609			85.9	5.19	541.25
610			92.4	5.6	591.13
611			89.7	5.45	554.23
612			88.7	5.58	582.28
613			93.2	6.06	649.24
614			94.1	5.55	592.18
615			90	5.09	571.23
616			93.3	5.91	577.26
617			91.4	4.53	582.24
618			92.1	5.84	553.22



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
619			76.6	5.06	490.15
620			91.2	5.56	539.99
621			86.7	5.39	503.12
622			81	5.47	531.15
623			92.2	6.13	598.06
624			84.8	5.59	541.03
625			88	5.04	520.11
626			91.6	5.91	526.14
627			89.4	4.49	531.11
628			90.3	5.89	502.10
629			83.3	4.41	458.20
630			91.5	4.72	508.08



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
631			87.8	4.57	471.18
632			57.7	4.71	499.23
633			92.8	5.54	566.12
634			93.5	4.93	509.13
635			89.3	4.29	488.19
636			93.6	4.99	494.21
637			91.7	3.88	499.21
638			91.9	5.22	470.18



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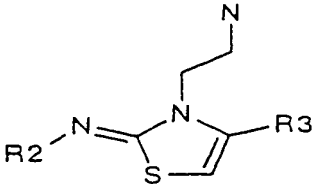
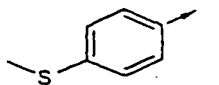
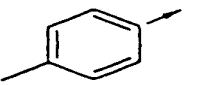
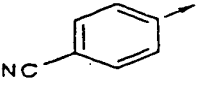
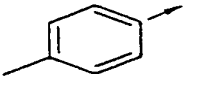
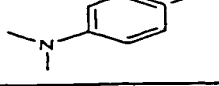
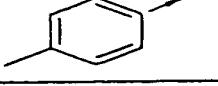
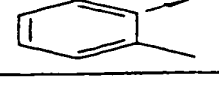


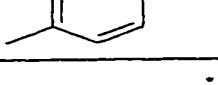
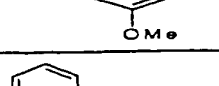
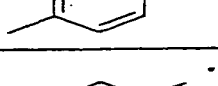
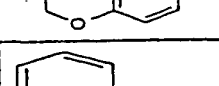
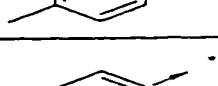
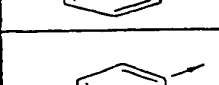
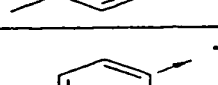
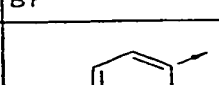
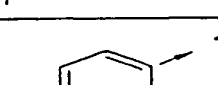
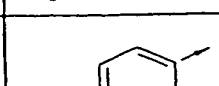
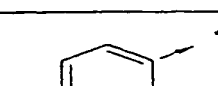

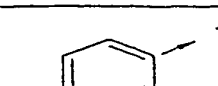


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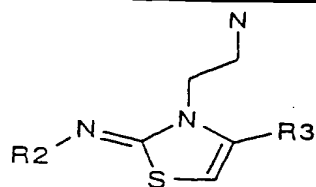
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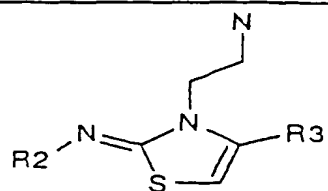
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
639			95	7.28	374.10
640			87	7.62	364.24
641			84	6.75	342.23
642			79	6.6	321.24
643			81	4.96	339.29
644			82	6.44	324.28
645			83	7.16	338.30
646			59	6.6	356.25
647			86	7.28	402.23
648			84	7.29	346.26
649			85	7.66	388.1
650			84	7.96	378.21



					
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
651			85	7.14	356.23
652			73	7.02	335.26
653			76	5.37	353.29
654			83	6.84	338.30
655			81	7.51	352.29
656			75	6.99	370.27
657			77	7.6	416.26
658			80	7.65	360.25
659			87	7.37	392.10
660			71	7.7	382.16
661			63	6.9	360.21
662			59	6.7	339.23



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
663			80	5.06	357.26
664			63	6.61	342.26
665			82	7.28	356.25
666			39	6.74	374.22
667			85	7.42	420.24
668			81	7.39	364.26
669			93	8.28	443.2
670			88	8.61	433.2
671			88	7.7	411.2
672			80	7.76	390.26
673			85	6.08	408.3
674			89	7.36	393.3

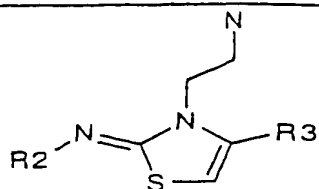


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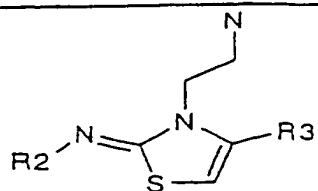
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
675			84	8.03	407.3
676			81	7.59	425.3
677			83	8.03	471.3
678			91	8.24	415.2



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
679			78	7.41	419.09
680			75	6.98	369.23
681			81	7.51	383.23
682			85	7.46	391.20
683			74	6.79	351.21
684			81	5.18	369.26
685			76	6.73	354.26
686			87	7.39	368.27
687			80	7.48	376.22
688			83	8.14	424.11
689			83	8.37	414.14
690			78	7.48	371.21
691			85	5.88	389.24
692			79	7.53	374.24

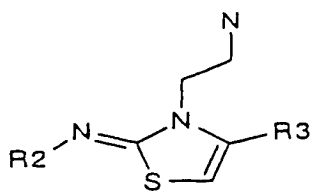


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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
693			83	8.1	388.23
694			77	8.18	452.23
695			81	8.14	396.20
696			76	7.94	413.16



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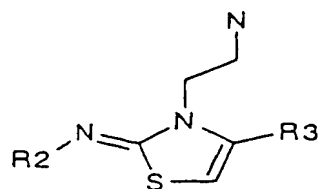
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
697			86	7.41	402.01
698			93	7.57	360.16
699			74	6.32	361.23
700			88	7.75	344.19
701			83	6.88	317.22
702			93	8.33	509.9
703			90	8.69	411.99
704			72	8.16	382.21
705			81	7.27	382.2
706			82	7.7	436.05
707			91	7.85	394.16
708			80	6.59	395.19



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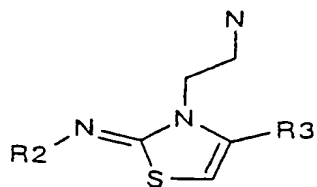
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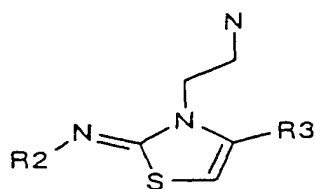
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
709			87	7.99	378.16
710			83	7.3	351.2
711			89	8.58	543.85
712			89	8.9	446.01
713			72	8.35	416.19
714			82	7.62	416.19
715			85	7.84	436.05
716			88	7.97	394.14
717			75	6.82	395.21
718			88	8.13	378.13
719			78	7.5	351.2
720			91	8.65	543.86



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
721			89	8.97	446.0
722			75	8.55	416.19
723			83	7.84	416.19
724			90	8.24	506.01
725			88	8.37	464.1
726			76	7.43	465.17
727			86	8.52	448.1
728			84	8.11	421.11
729			89	8.97	613.8
730			90	9.24	515.94
731			74	8.94	486.17
732			81	8.51	486.16





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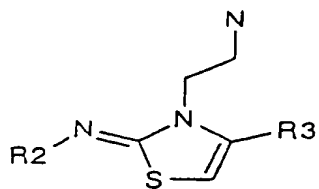
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
733			82	8.15	584.93
734			81	8.26	543.05
735			69	7.31	544.1
736			80	8.43	527.07
737			82	7.99	500.1
738			88	8.92	692.79
739			85	9.23	594.87
740			71	8.84	565.1
741			79	8.36	565.08
742			82	7.77	475.06
743			81	7.91	433.13
744			86	6.72	434.21



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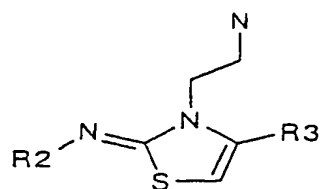
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Ex.	R2	R3	Purity (%)	<i>n</i> (min.)	[M+H] <sup>+</sup>
745			82	8.03	417.15
746			74	7.32	390.17
747			86	8.61	582.85
748			76	8.94	485.01
749			73	8.33	455.19
750			84	7.59	455.2
751			67	8.82	525.96
752			75	8.93	484.08
753			68	8.08	485.14
754			75	9.08	468.06
755			78	8.77	441.06
756			81	9.56	633.79

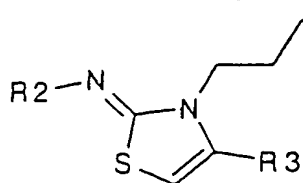


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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
757			81	9.77	535.91
758			70	9.55	506.12
759			78	9.21	506.13

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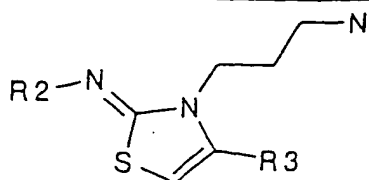
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
760			92.9	5.03	436.23
761			90.4	5.56	422.33
762			94.36	4.94	420.26
763			88.08	5.09	428.30
764			77.6	4.42	423.34
765			92.4	5.52	480.38
766			84.6	4.8	402.25
767			89.8	5.79	462.37
768			91.9	5.12	460.20
769			91.4	5.14	476.21
770			94.2	5.67	514.18
771			93,0	5.37	464.18



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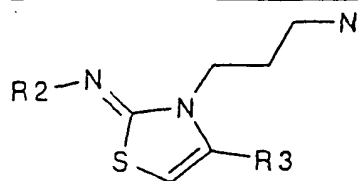
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
772			94.5	5.64	572.07
773			87.9	5.76	522.21
774			91.2	5.12	474.23
775			78.1	5.82	530.27
776			88.8	4.55	408.22
777			90.7	5.13	394.34
778			92.6	4.45	392.23
779			88.8	4.65	400.30
780			76.5	3.94	395.33
781			90.8	5.11	452.38
782			87.7	4.33	374.29
783			91.5	5.35	434.38



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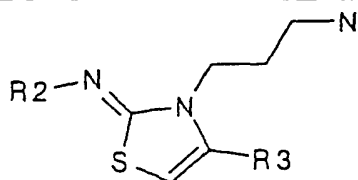
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
784			92.1	4.61	424.25
785			89.3	5.28	410.33
786			95	4.49	408.22
787			82.4	4.74	416.27
788			73.8	3.95	411.30
789			92.9	5.27	468.36
790			84.9	4.39	390.28
791			91.5	5.53	450.37
792			90	5.5	462.19
793			93.9	6.25	448.31
794			94.9	5.41	446.22
795			93.5	5.76	454.26



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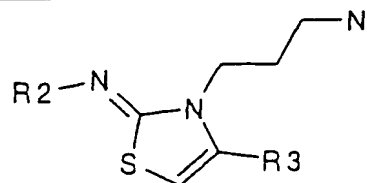
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
796			89.8	4.95	449.30
797			92.4	6.22	506.34
798			93	5.52	428.245
799			92.8	6.39	488.34
800			87.6	5.11	412.20
801			92.5	5.9	398.30
802			93.5	5	396.20
803			92.2	5.35	404.26
804			90.7	4.41	399.28
805			94.2	5.87	456.34
806			89.3	5.05	378.23
807			90.9	6.07	438.33



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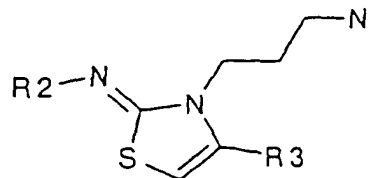
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
808			88.8	5.43	520.09
809			94	6.19	506.19
810			95.9	5.33	504.12
811			92.9	5.68	512.15
812			88.9	4.8	507.18
813			92.3	6.17	564.20
814			93.9	5.41	486.14
815			93.5	6.35	546.18
816			91.9	5.41	470.25
817			93	5.98	456.34
818			91.4	5.29	454.24
819			90.4	5.49	462.29





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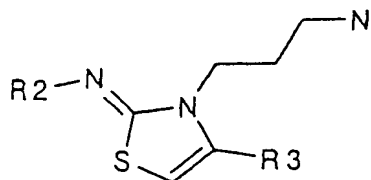
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
820			86.5	4.75	457.34
821			90.5	5.94	514.34
822			90.1	5.21	436.26
823			89.7	6.18	496.37
824			79.4	4.56	422.22
825			92.5	5.08	408.32
826			93	4.45	406.23
827			90.2	4.63	414.26
828			76.3	4.01	409.31
829			94	5.08	466.36
830			90.7	4.34	388.25
831			92.9	5.29	448.36



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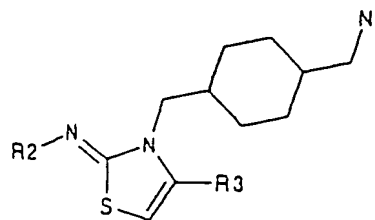
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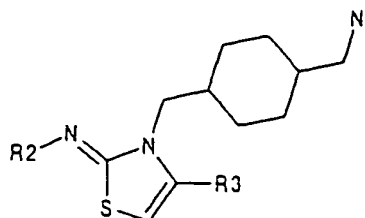
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
832			56	5.3	478.29
833			83.9	5.7	464.38
834			82.1	5.19	462.29
835			80.5	5.31	470.35
836			70.6	4.8	465.39
837			82.9	5.67	522.41
838			81	5.07	444.33
839			83.5	5.91	504.41



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
840			35 + 64	3.68 + 3.78	423.2
841			98	3.7	438.3
842			35 + 63	4.3 + 4.4	446.2
843			97	3.71	436.3
844			32 + 65	3.28 + 3.34	447.3
845			96	3.84	392.3
846			96	4.18	447.3
847			30 + 64	3.62 + 3.64	475.3
848			36 + 61	4.46 + 4.61	418.3
849			96	5.89	569.1
850			94	6.09	584.2
851			57 + 39	6.55 + 6.6	592.1



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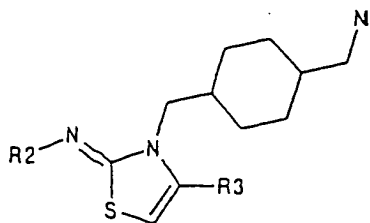
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
852			96	6.16	582.2
853			28 + 59	5.53 + 5.61	593.2
854			95	6.35	538.2
855			54 + 41	6.8 + 6.88	593.3
856			94	5.96	621.2
857			56 + 39	6.46 + 6.55	564.2
858			34 + 63	4.09 + 4.2	451.3
859			96	4.03	466.4
860			33 + 64	4.69 + 4.76	474.3
861			27 + 70	4.04 + 4.07	464.4
862			33 + 63	3.63 + 3.71	475.4
863			95	4.18	420.4



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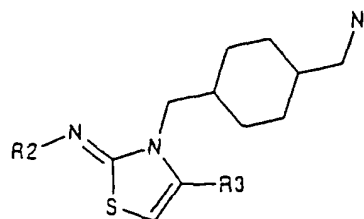
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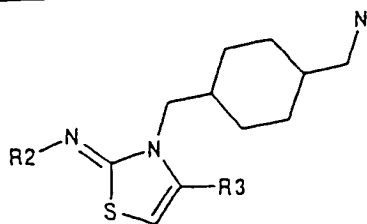
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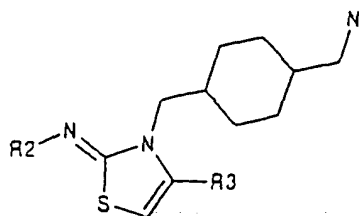
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
864			89	4.46	475.4
865			22 + 68	3.94 + 3.98	503.4
866			35 + 62	4.9 + 5.01	446.4
867			35 + 61	4.39 + 4.52	487.3
868			33 + 63	4.22 + 4.29	502.3
869			35 + 62	5.08 + 5.2	510.2
870			31 + 63	4.26 + 4.34	500.3
871			33 + 62	3.82 + 3.91	511.3
872			31 + 62	4.42 + 4.51	456.3
873			29 + 64	4.66 + 4.72	511.4
874			33 + 57	4.11 + 4.2	539.3
875			35 + 62	5.26 + 5.39	482.3



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
876			32 + 65	3.63 + 3.7	467.3
877			97	3.69	482.4
878			35 + 62	4.2 + 4.28	490.3
879			94	3.69	480.3
880			28 + 68	3.3 + 3.33	491.3
881			96	3.8	436.3
882			96	4.18	491.4
883			94	3.63	519.3
884			36 + 61	4.28 + 4.42	462.3
885			36 + 62	4.24 + 4.36	517.3
886			28 + 69	4.15 + 4.21	532.3
887			35 + 62	4.84 + 4.96	540.2

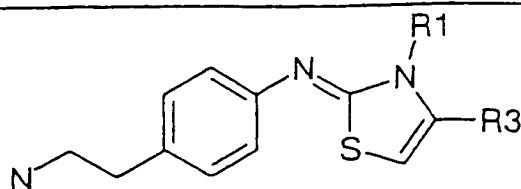


Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
888			33 + 64	4.15 + 4.22	530.3
889			32 + 63	3.76 + 3.84	541.3
890			32 + 63	4.28 + 4.36	486.3
891			24 + 73	4.56 + 4.6	541.3
892			31 + 59	4.05 + 4.11	569.3
893			35 + 61	4.99 + 5.14	512.3
894			33 + 64	5.59 + 5.7	576.3
895			35 + 61	5.29 + 5.39	591.3
896			26 + 71	6.32 + 6.35	599.2
897			34 + 63	5.41 + 5.5	589.3
898			35 + 61	4.88 + 4.99	600.3
899			35 + 62	5.63 + 5.72	545.3



Ex.	R2	R3	Purity (%)	rt (min)	[M+H] <sup>+</sup>
900			34 + 61	5.76 + 5.86	600.3
901			34 + 68	5.16 + 5.28	628.3
902			98	6.45	571.3
903			35 + 60	3.84 + 3.93	502.3
904			32 + 62	3.72 + 3.79	517.3
905			32 + 62	4.59 + 4.68	525.2
906			33 + 61	3.75 + 3.82	515.3
907			29 + 64	3.18 + 3.26	526.3
908			32 + 59	4 + 4.09	471.3
909			32 + 60	4.28 + 4.38	526.3
910			34 + 56	3.62 + 3.71	554.3
911			31 + 63	4.58 + 4.66	497.3





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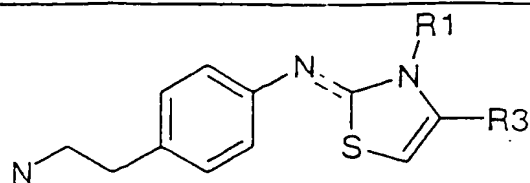
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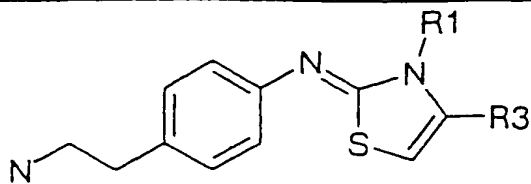
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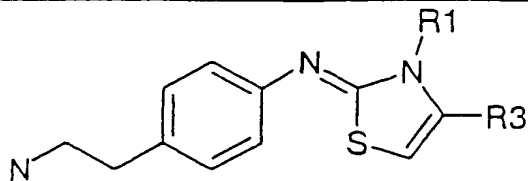
Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
912			6.8 + 91.2	3.6 + 3.76	332.22
913			88.1	3.94	352.19
914			89.6	4.22	380.22
915			61.6	3.95	382.17
916			83.5	3.8	377.19
917			84.2	4.41	430.10
918			70.9	4.24	393.18
919			84.1	4.1	397.16
920			82.2	4.55	436.05
921			82.8	4.66	392.17
922			98	4.25	380.22
923			91.1	4.26	400.17



Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
924			92.4	4.46	428.21
925			93.8	4.23	430.20
926			86.4	4.14	425.17
927			92.3	4.7	478.11
928			82	4.56	441.18
929			90.9	4.44	445.18
930			89.8	4.9	484.07
931			86.4	5.0	440.17
932			97.2	4.38	394.22
933			86.3	4.48	414.18
934			92.6	4.68	442.22
935			91	4.44	444.22



Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
936			85.9	4.34	439.18
937			88.2	4.86	492.12
938			83.6	4.71	455.2
939			87.8	4.59	459.19
940			89.8	5.0	498.09
941			83.9	5.14	454.20
942			87.7	4.26	384.17
943			94.7	4.5	404.15
944			18.6 + 76.4	4.2 + 4.64	432.18
945			95.2	4.32	434.16
946			92	4.46	429.15
947			94.4	5.08	482.06



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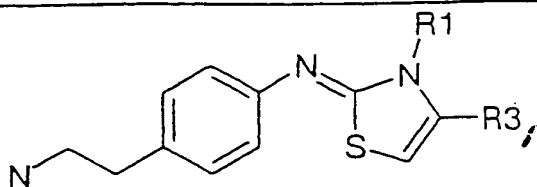
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
948			93	4.86	445.16
949			94.2	4.82	449.13
950			93.1	5.34	488.03
951			93.7	5.47	444.16
952			91.5	4.43	400.13
953			95	4.82	420.12
954			14.8 + 81.2	4.38 + 4.88	448.15
955			95.8	4.64	450.13
956			95	4.79	445.11
957			95.4	5.4	498.06
958			93.9	5.14	461.12
959			94.5	5.12	465.10



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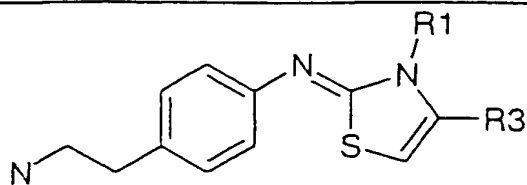
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
960			94.6	5.62	504.00
961			96.4	5.74	460.13
962			6.5 + 87.5	4.2 + 4.54	416.19
963			92.9	4.76	436.17
964			17.3 + 6.2	4.5 + 4.9	464.21
965			92.6	4.64	466.17
966			89	4.76	461.16
967			94.1	5.32	514.09
968			92.1	5.09	477.19
969			90.5	5.1	481.16
970			92	5.56	520.02
971			93	5.72	476.17



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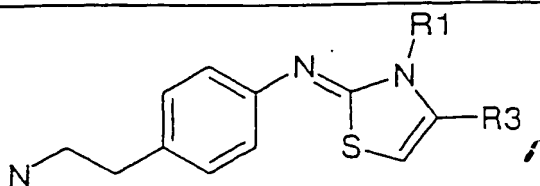
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
972			91.6	4	410.16
973			89.7	4.28	430.15
974			83.4	4.46	458.19
975			96.9	4.19	460.16
976			58.2	4.29	455.12
977			81.4	4.84	508.06
978			85.8	4.64	471.15
979			46.8	4.62	475.14
980			77.4	5.06	514.02
981			61.7	5.24	470.16
982			4.8	3.54	356.15
983			71.4	4.1	376.14



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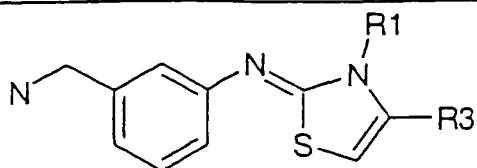
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
984			79	4.3	404.17
985			88.3	4.0	406.13
986			12.2	5.32	401.11
987			46.5	4.72	454.04
988			56.3	4.49	417.15
989			13.8	5.52	421.12
990			35.3	4.95	460.02
991			9.1	5.71	416.11



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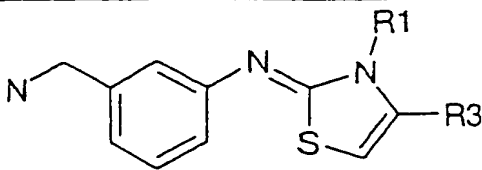

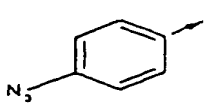
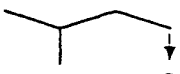
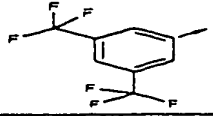
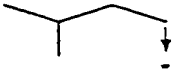
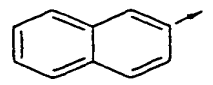
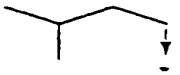
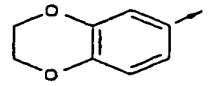
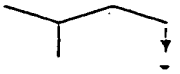
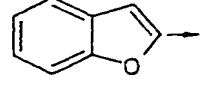
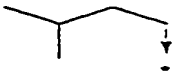
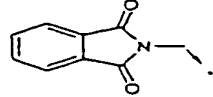

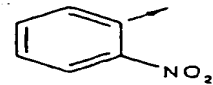



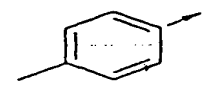
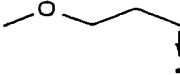
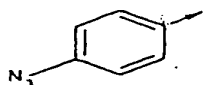
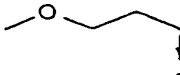
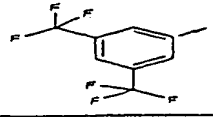
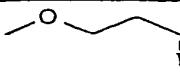
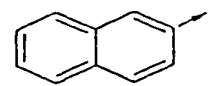
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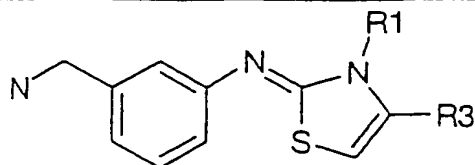
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
992			95.3	3.33	367.12
993			91.9	3.97	400.03
994			92.5	3.64	336.17
995			83.7	3.75	363.13
996			94.7	4.88	458.11
997			93.1	4.03	372.14
998			92.6	3.37	380.14
999			92.1	4.36	362.12
1000			91	3.32	405.11
1001			87.8	3.9	397.14
1002			64.2	4.46	430.09
1003			61.6	4.18	366.23



					
Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1004			45.6	4.26	393.16
1005			72.4	5.28	488.17
1006			67	4.47	402.17
1007			51.1	3.86	410.16
1008			57.6	4.86	392.16
1009			75.1	3.92	435.16
1010			90.7	3.24	399.13
1011			79.6	3.79	432.06
1012			74.5	3.55	368.16
1013			58.8	3.62	395.15
1014			81	4.65	490.15
1015			86.8	3.88	404.17



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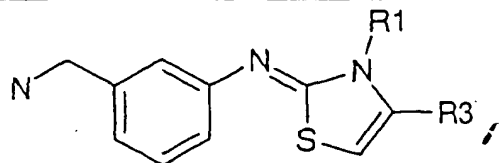
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1016			71.4	3.3	412.13
1017			73.7	4.13	394.15
1018			80.5	3.3	437.15
1019			94.6	4.19	417.10
1020			94.8	4.76	450.07
1021			92.9	4.42	386.13
1022			88.8	4.56	413.11
1023			94.1	5.48	508.13
1024			93.8	4.79	422.13
1025			92.3	4.04	430.15
1026			90	5.08	412.10
1027			93.2	3.95	455.13



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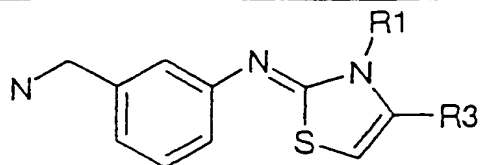
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1028			92.6	4.3	435.1
1029			92.8	4.9	470.1
1030			89.2	4.6	404.1
1031			89.2	4.76	431.1
1032			94.3	5.6	526.1
1033			93.5	5	440.2
1034			92.4	4.2	448.1
1035			87.9	5.2	430.1
1036			93.6	4.1	473.2
1037			80.4	4.16	447.14
1038			72.7	4.72	480.08
1039			77	4.39	416.14



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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1040			59.2	4.5	443.16
1041			16.8	5.98	538.12
1042			59.5	4.74	452.16
1043			74	4.02	460.16
1044			26.3	5.52	442.13
1045			91	3.82	485.17
1046			89.8	5.09	507.19
1047			84.5	5.52	540.09
1048			86	5.06	476.21
1049			75.6	5.22	503.21
1050			90.3	6.14	598.15
1051			85.9	5.38	512.22

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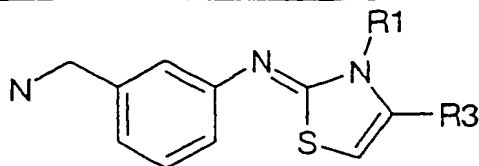
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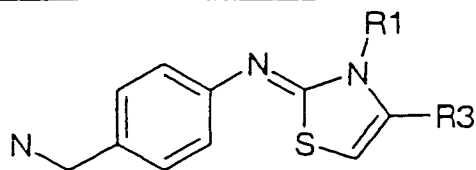
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1052			81.3	4.68	520.19
1053			83.3	5.66	502.20
1054			82	4.92	545.17
1055			93.1	4.34	445.16
1056			81.5	4.77	478.10
1057			79.9	4.46	414.17
1058			70.2	4.56	441.15
1059			85.8	5.56	536.11
1060			84.1	4.73	450.19
1061			78.4	4.12	458.20
1062			83.3	5.13	440.16
1063			83.1	4.22	



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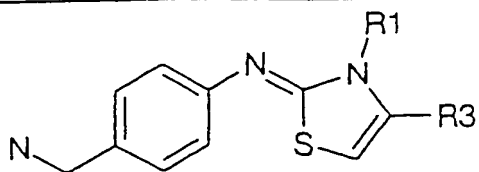
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1064			86.6	3.52	338.12
1065			90.4	3.44	383.09
1066			87.3	4.25	422.10
1067			85.9	4.04	416.04
1068			70.5	4.4	444.18
1069			80.1	4.83	474.13
1070			80.6	4.34	402.16
1071			80.8	4.37	378.14
1072			86.5	4.77	442.06
1073			83.4	4.72	405.12
1074			90.5	3.02	340.15
1075			93.5	2.98	385.10



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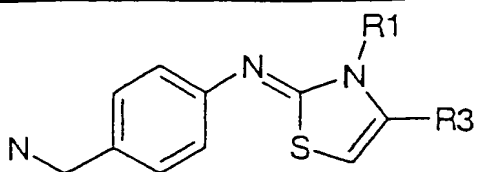
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1076			91.7	3.9	424.12
1077			90.8	3.62	418.04
1078			80.8	4.09	446.18
1079			88.1	4.6	476.12
1080			91.5	3.98	404.16
1081			89.2	3.87	380.13
1082			87.3	4.36	444.10
1083			90.6	4.24	407.13
1084			86.4	4.24	414.15
1085			91.8	4.21	459.17
1086			88.2	4.89	498.19
1087			85.8	4.71	492.12



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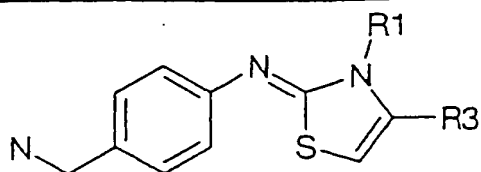
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1088			76.1	4.9	520.21
1089			83.3	5.45	550.17
1090			84.9	4.9	478.24
1091			86.1	5.08	454.19
1092			78	5.38	518.14
1093			84.5	5.38	481.21
1094			37.5	3.36	386.14
1095			57.1	3.35	431.14
1096			44	3.78	470.17
1097			42	3.62	464.09
1098			38.8	4.14	492.21
1099			45.2	3.98	522.14





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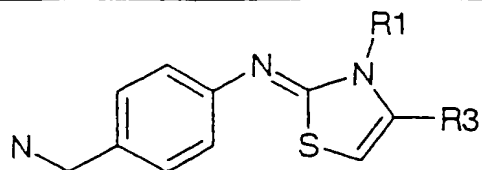
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1100			33.4	3.99	450.20
1101			44.7	3.68	426.14
1102			33.4	4.08	490.12
1103			42.4	3.67	453.17
1104			92.6	4.23	390.14
1105			91.9	4.1	439.1
1106			92.1	5	474.13
1107			93	4.85	468.04
1108			86.5	5.04	496.18
1109			92.8	5.5	526.13
1110			92.8	5.1	454.17
1111			92	5.1	430.10



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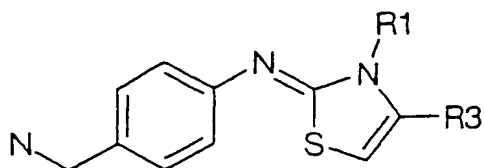
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1112			92.8	5.48	494.08
1113			92.8	5.1	457.18
1114			93.8	4.6	406.10
1115			93.6	4.5	451.03
1116			93.1	5.2	490.10
1117			94.5	5.1	483.99
1118			89.54	5.29	512.13
1119			95.2	5.6	542.1
1120			92.8	5.38	470.15
1121			93.4	5.3	445.94
1122			94.7	5.7	510.05
1123			94.3	5.3	473.04



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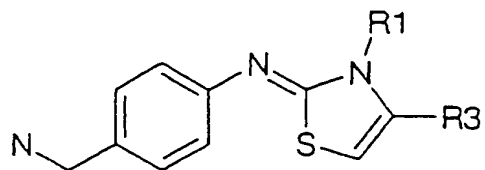
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1124			89.5	4.06	400.12
1125			92.1	4.13	445.13
1126			88.9	4.81	484.15
1127			88.8	4.56	478.09
1128			82.4	4.76	506.20
1129			88.6	5.36	536.12
1130			85.7	4.78	464.18
1131			84	4.94	440.15
1132			64.3	5.38	504.10
1133			88.4	5.16	467.17
1134			82.7	3.76	446.16
1135			89	3.77	491.14



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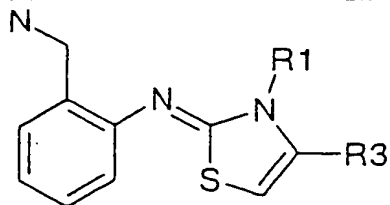
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1136			87.1	4.4	530.13
1137			84.6	4.21	524.08
1138			76	4.52	552.19
1139			85.6	4.98	582.12
1140			83.1	4.44	510.21
1141			88.3	4.6	486.19
1142			1.5	5.07	550.12
1143			84	4.75	513.16



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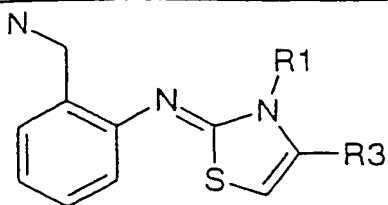
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Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1144			75	4.48	300.16
1145			82	4.89	348.16
1146			86.7	4.72	354.09
1147			89	4.96	398.01
1148			87	4.37	345.18
1149			90	5.4	396.1
1150			89	5.9	448.2
1151			85	5	404
1152			85	4.96	360.10
1153			91	4.39	417.14
1154			95	5.14	366.21
1155			92	5.52	414.17



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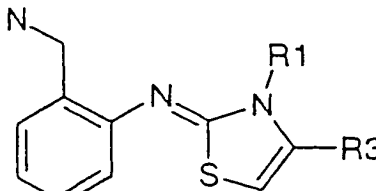
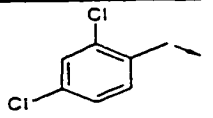
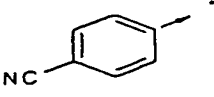
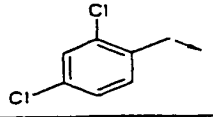
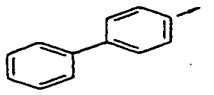
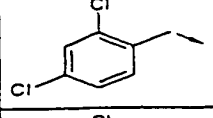
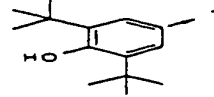
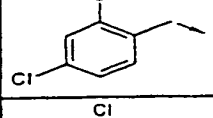
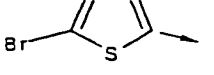
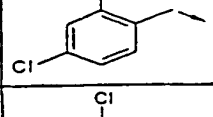
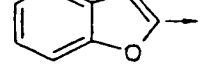
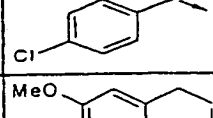
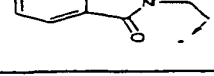
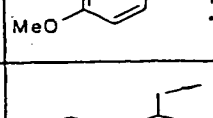
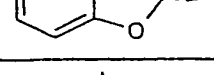
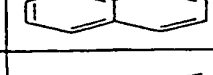

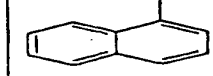
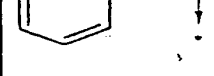
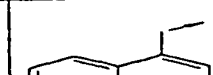

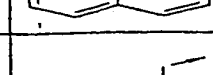
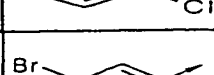
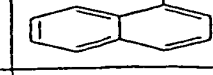
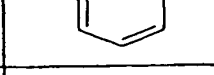
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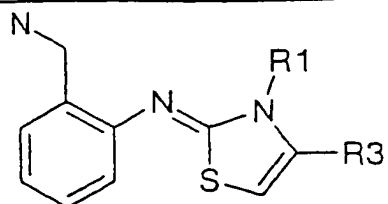
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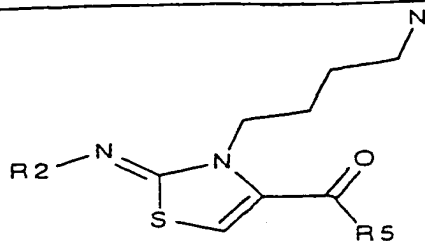
Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1156			95	5.37	420.13
1157			93	5.6	464.08
1158			94	5	411.2
1159			91	6.04	462.19
1160			91.5	6.4	514.2
1161			92.6	5.7	470.1
1162			93.8	5.6	426.14
1163			91.4	5.02	483.21
1164			96.3	5.55	420.10
1165			78.2	5.81	468.10
1166			96.7	5.6	474.06
1167			96.9	5.8	517.97

					
Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1168			94.2	5.18	465.06
1169			94	6.25	516.10
1170			96.4	6.52	568.2
1171			94.6	5.9	524.0
1172			94.9	5.81	480.07
1173			91.9	5.25	537.09
1174			77.4	5.24	486.16
1175			96.8	5.36	402.15
1176			92.4	5.66	450.19
1177			93.3	5.48	456.12
1178			93.3	5.7	500.08
1179			90.7	5.12	447.15

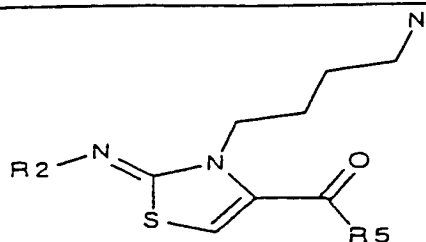


Ex.	R1	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1180			91.9	6.12	498.21
1181			95.1	6.5	550.3
1182			92.8	5.7	506.0
1183			94.9	5.74	462.15
1184			91.4	5.13	519.17
1185			73.6	3.52	346.19
1186			71.5	4.5	394.17
1187			82.2	4.58	400.10
1188			78.6	4.86	444.09
1189			70.5	5.3	442.17
1190			76.8	5	406.13
1191			80.5	4.1	463.19

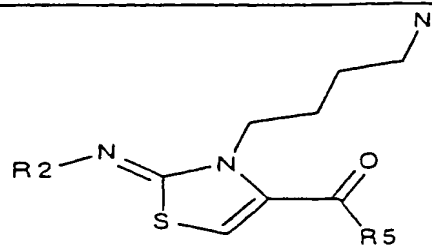




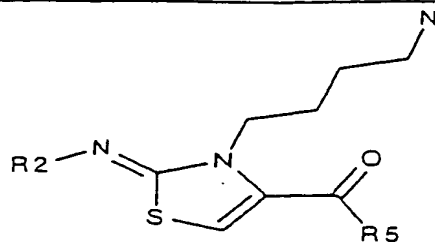
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1192			28.3	3.61	373.15
1193			64.3	2.55	396.15
1194			66.8	3.58	425.13
1195			51.9	3.47	387.07
1196			75.8	4.43	471.21
1197			66.4	2.38	399.15
1198			42.6	3.11	474.14
1199			45.3	4.39	457.18
1200			64	4.62	485.21
1201			55.1	4.09	429.12
1202			75	4.22	449.13
1203			67.9	3.64	417.11



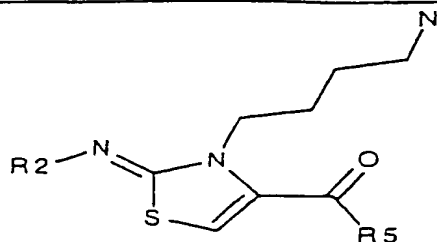
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1204			31.7 + 17.3	4.65 + 4.8	429.24
1205			41.8	3.86	407.14
1206			67.8	4.58	487.20
1207			33.2	4.31	415.20
1208			60.9	3.29	438.21
1209			58	4.29	467.18
1210			51.9	4.21	429.15
1211			70	5.03	513.24
1212			22.9	3.17	441.19
1213			71.8	3.81	516.16
1214			35.4	5.03	499.23
1215			64	5.18	527.25



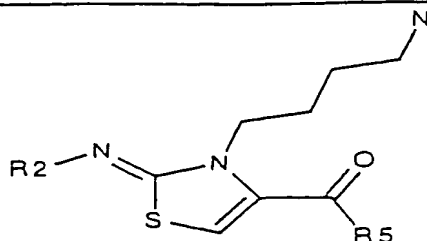
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1216			68.2	4.71	471.19
1217			76.5	4.84	491.18
1218			67.6	4.35	459.16
1219			28.7 + 14.2	5.27 + 5.4	471.30
1220			66.9	4.52	449.21
1221			64.1	5.17	529.21
1222			49.7	4.55	423.19
1223			78.8	3.41	446.17
1224			76.2	4.48	475.15
1225			68.3	4.42	437.12
1226			79.6	5.24	521.17
1227			49.1	3.29	449.20



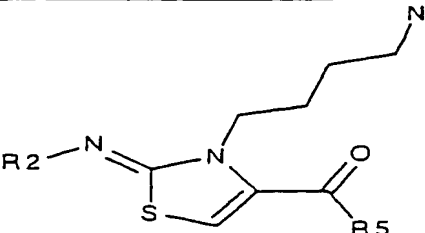
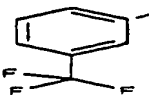
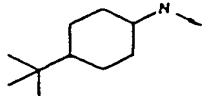
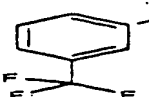
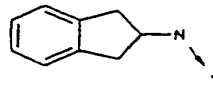

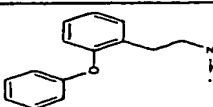
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1228			72.2	4	524.15
1229			69.7	5.22	507.20
1230			75	5.42	535.20
1231			78	4.93	479.13
1232			79.1	5.04	499.16
1233			82.6	4.56	467.13
1234			45 + 24.6	5.53 + 5.7	479.26
1235			77	4.75	457.18
1236			70.4	5.41	537.18
1237			47.7	4.38	407.12
1238			71.3	3.27	430.12
1239			70.2	4.35	459.10

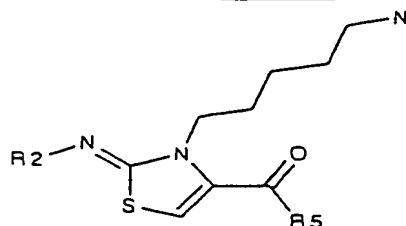


Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1240			68.1	4.27	421.06
1241			78.8	5.13	505.13
1242			24	3.17	433.11
1243			74.2	3.86	508.08
1244			43	5.16	491.08
1245			71.8	5.38	519.12
1246			69.9	4.85	463.05
1247			79.2	4.96	483.10
1248			77.9	4.45	451.07
1249			42.6 + 23.5	5.42 + 5.6	463.20
1250			70	4.65	441.11
1251			72	5.36	521.12



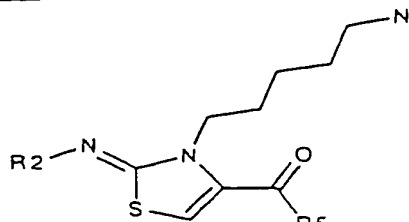
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1252			28.2	4.96	441.14
1253			65.8	3.69	464.14
1254			51	4.86	493.14
1255			64.5	4.79	455.08
1256			72.2	5.55	539.16
1257			27.2	3.59	467.16
1258			38.6	4.38	542.12
1259			49.4	5.53	525.16
1260			60.6	5.73	553.20
1261			67.7	5.27	497.13
1262			80.8	5.34	517.12
1263			78	4.92	485.13

					
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1264			28.5 + 14.4	5.87 + 6.0	497.26
1265			60.5	5.13	475.16
1266			65.7	5.73	555.14

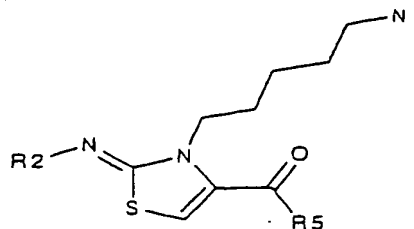


Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1267			60	3.86	439.18
1268			88.1	2.89	478.24
1269			89.1	3.83	389.20
1270			94.3	2.41	396.14
1271			94	2.33	418.20
1272			80.3	4.05	533.17
1273			93	4.33	485.23
1274			90.5	4.27	471.22
1275			82.4	3.94	423.20
1276			92.8	4.07	487.10
1277			92.3	4.09	463.16
1278			90.6	2.9	430.20

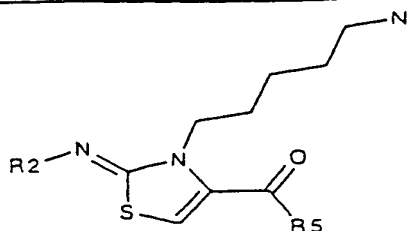




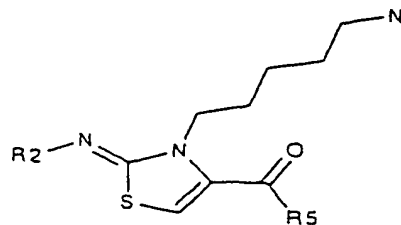
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1279			94.7	3.69	431.14
1280			90.6	4.37	471.21
1281			86.4	4.51	501.20
1282			93.1	4.16	463.09
1283			63.6	5.58	541.11
1284			82.4	4.23	580.17
1285			87.6	5.63	491.16
1286			91.5	4.03	498.13
1287			89.5	3.91	520.13
1288			82.2	5.61	635.14
1289			92.3	5.9	587.14
1290			89.9	5.86	573.11



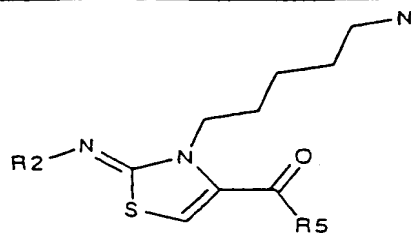
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1291			90	5.66	525.14
1292			90.9	5.73	589.02
1293			91.2	5.69	565.07
1294			89.4	4.72	532.13
1295			93.3	5.44	533.08
1296			93.1	5.95	573.11
1297			90.1	6.06	603.16
1298			90.3	5.79	565.00
1299			63.6	4.65	515.20
1300			82.9	3.63	554.24
1301			85.9	4.67	465.23
1302			85.4	3.41	472.20



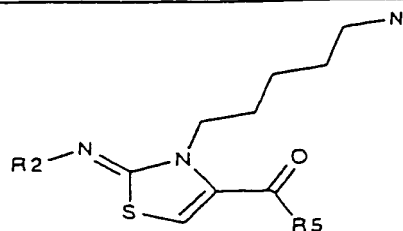
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1303			83.7	3.31	494.23
1304			84.2	4.79	609.20
1305			86.5	5.11	561.20
1306			84.2	5.11	547.19
1307			84.8	4.75	499.23
1308			89	4.89	539.15
1309			85.9	3.76	506.23
1310			88.5	4.59	507.17
1311			87.8	5.16	547.20
1312			1.5	5.6	577.22
1313			89.7	4.99	539.10
1314			65.3	4.81	545.20



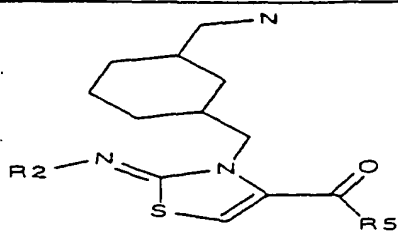
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1315			86.7	3.82	584.25
1316			87.6	4.81	495.24
1317			91	3.63	502.20
1318			90.2	3.54	524.24
1319			85.4	4.91	639.22
1320			85.7	5.21	591.23
1321			90	5.19	577.22
1322			87.9	4.87	529.22
1323			86.4	5	593.12
1324			87.5	5.01	569.16
1325			89.7	4	536.23
1326			89.6	4.73	537.18



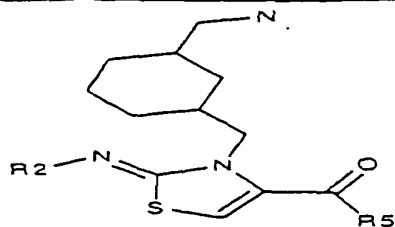
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1327			89.6	5.24	577.24
1328			86.7	5.33	607.24
1329			90.6	5.1	569.10
1330			62.1	4.17	467.23
1331			92.8	3.23	506.28
1332			81.3	4.14	417.24
1333			91.9	2.95	424.19
1334			91.8	2.87	446.24
1335			78.7	4.31	561.19
1336			89.5	4.58	513.25
1337			91.3	4.54	499.24
1338			80.3	4.24	451.23



Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1339			77.6	4.37	515.12
1340			85.7	4.37	491.18
1341			92.3	3.34	458.25
1342			90.8	4.05	459.19
1343			79.9	4.63	499.25
1344			76.6	4.75	529.24
1345			91.9	4.45	491.13

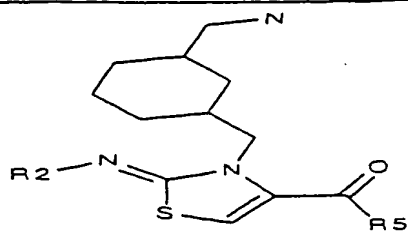


Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1346			56.9 + 24.5	4.07 + 4.2	417.23
1347			64.6 + 24.4	4.98 + 5.1	526.30
1348			62.4 + 25.1	3.96 + 4.1	430.25
1349			80.5	3.44	490.37
1350			65.4 + 27.8	4.9 + 5.0	503.31
1351			64.5 + 25.5	5.6 + 5.7	536.35
1352			86.8	3.3	509.30
1353			64.1 + 29.8	5.02 + 5.1	537.26
1354			60.8 + 32.2	5.37 + 5.5	543.32
1355			59.6 + 31.5	5.24 + 5.3	545.30
1356			61.6 + 24.8	4.69 + 4.8	527.31
1357			88.7	3.8	536.36

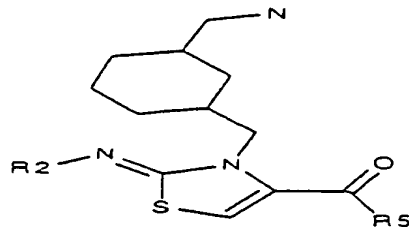


Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1358			87.5	3.8	528.38
1359			58 + 25.2	4.12 + 4.3	417.27
1360			68.1 + 24.5	5.22 + 5.3	529.31
1361			64.8 + 23.1	5.12 + 5.2	535.19
1362			61.9 + 21.6	5.46 + 5.5	535.23
1363			90.4	6.06	644.33
1364			89.7	5.31	548.24
1365			84.3	4.5	608.34
1366			95.2	6.06	621.27
1367			90.9	6.6	654.4
1368			84.2	4.41	627.29
1369			92.8	6.12	655.27

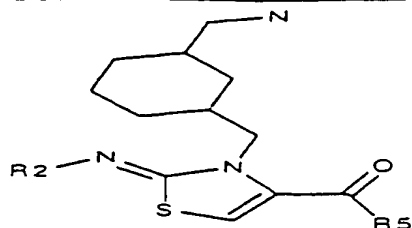




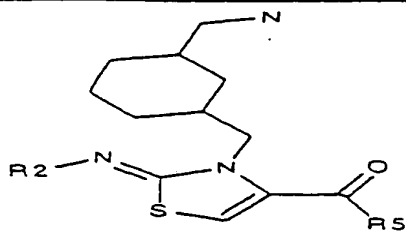
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1370			91.9	6.4	661.33
1371			93.2	6.3	663.32
1372			87.3	5.9	645.32
1373			87.5	4.7	654.4
1374			84.8	4.7	646.38
1375			71.8	5.53	535.23
1376			94.2	6.28	647.32
1377			91.6	6.25	653.22
1378			63 + 26.1	3.98 + 4.2	441.30
1379			64.5 + 28	4.8 + 5.0	550.36
1380			65.1 + 26.9	3.93 + 4.1	454.30
1381			56.6 + 30.1	3.54 + 3.6	514.40



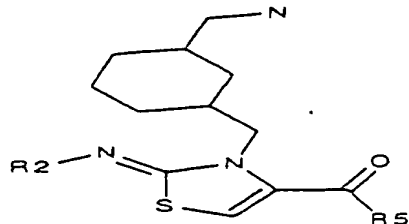
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1382			64.8 + 30.3	4.64 + 4.9	527.34
1383			64.3 + 28.3	5.33 + 5.6	560.39
1384			64.5 + 24.8	3.5 + 3.6	533.35
1385			62.9 + 27.5	4.77 + 5.0	561.29
1386			48.5 + 20.8	5.08 + 5.3	567.36
1387			61.2 + 27.5	4.98 + 5.2	569.33
1388			58.4 + 22.7	4.5 + 4.7	551.36
1389			65.1 + 26.4	3.92 + 4.0	560.38
1390			63.6 + 26.1	3.92 + 4.1	552.43
1391			64 + 27.3	4.01 + 4.2	441.30
1392			66.2 + 28.9	4.96 + 5.2	553.35
1393			62.8 + 26.6	4.84 + 5.0	559.23



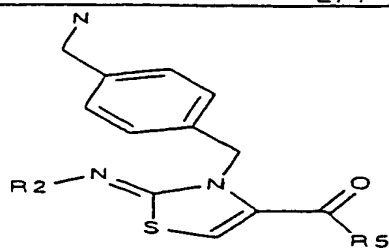
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1394			59.4 + 26.3	3.95 + 4.1	445.26
1395			63.7 + 28.7	4.89 + 5.1	554.28
1396			62 + 27.9	3.9 + 4.1	458.27
1397			58.9 + 28.7	3.48 + 3.5	518.35
1398			62.9 + 29.3	4.75 + 5.0	531.28
1399			63.2 + 28.4	5.46 + 5.7	564.32
1400			58.3 + 30.4	3.39 + 3.5	537.30
1401			61.8 + 28.3	4.88 + 5.0	565.23
1402			61.5 + 27.9	5.2 + 5.4	571.28
1403			62.2 + 29.5	5.09 + 5.3	573.28
1404			60.6 + 26.7	4.54 + 4.7	555.30
1405			59.2 + 31.8	3.86 + 4.0	564.32



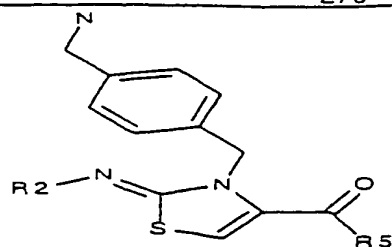
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1406			59.3 + 31.2	3.86 + 4.0	556.37
1407			49.3 + 21.7	4 + 4.2	445.26
1408			64.4 + 29.7	5.07 + 5.3	557.28
1409			61.7 + 27.9	4.96 + 5.1	563.20
1410			62.4 + 25.4	5.24 + 5.4	552.27
1411			63.6 + 28.1	5.91 + 6.0	661.33
1412			60.5 + 30.2	5.14 + 5.2	565.25
1413			87.2	4.43	625.36
1414			60.9 + 31.9	5.88 + 6.0	638.30
1415			61.1 + 31.2	6.47 + 6.6	671.37
1416			89.3	4.34	644.35
1417			66.6 + 25.7	5.96 + 6.0	672.28



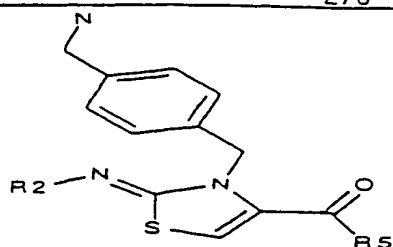
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1418			65.1 + 25.4	6.25 + 6.3	678.35
1419			63 + 27.5	6.13 + 6.2	680.32
1420			54.7 + 29.8	5.75 + 5.8	662.33
1421			91.7	4.71	671.38
1422			89.3	4.72	663.41
1423			49 + 23.9	5.34 + 5.4	552.26
1424			64.1 + 27.2	6.18 + 6.2	664.34
1425			62.3 + 27.3	6.13 + 6.2	670.25



Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1426			78.4	4.58	463.27
1427			53.4	4.48	471.23
1428			86.2	3.67	526.29
1429			86	4.58	542.25
1430			84.9	4.98	546.21
1431			42.9	3.26	494.27
1432			84.4	4.14	522.26
1433			83.2	4.72	570.25
1434			87.1	4.04	530.22
1435			45.6	3.16	464.25
1436			85.6	4.4	475.20
1437			84.2	4.96	541.18

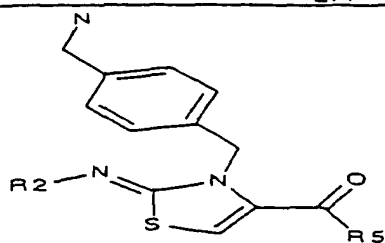


Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1438			87.2	3.88	554.28
1439			84.5	4.39	437.23
1440			33.8	5.34	593.17
1441			9.5	4.7	463.24
1442			78.8	5.11	499.20
1443			46.9	4.98	507.17
1444			87.9	3.88	562.19
1445			85.6	4.95	578.19
1446			84.9	5.3	582.14
1447			49	3.45	530.19
1448			81.4	4.62	558.18
1449			83	5.06	606.20

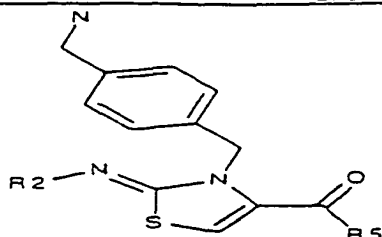


Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1450			84.9	4.42	566.15
1451			40.7	3.5	500.19
1452			85.1	4.87	511.13
1453			87.4	5.33	577.13
1454			85.6	4.08	590.24
1455			54.9	4.92	473.21
1456			43	5.66	629.13
1457			17.2	5.2	499.20
1458			77.6	4.3	479.20
1459			55.3	4.2	487.18
1460			85.2	3.32	542.22
1461			87	4.22	558.19

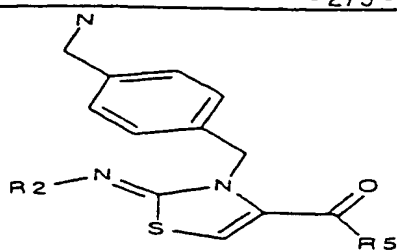




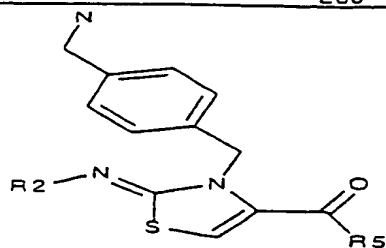
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1462			85.9	4.64	562.14
1463			82.9	2.74	510.23
1464			81.6	3.84	538.20
1465			84.1	4.41	586.21
1466			85.5	3.66	546.16
1467			49.3	2.8	480.20
1468			81.7	4.11	491.15
1469			83.7	4.71	557.14
1470			82.2	3.59	570.24
1471			66.1	4.11	453.19
1472			29.5	5.12	609.14
1473			9.9	4.44	479.20



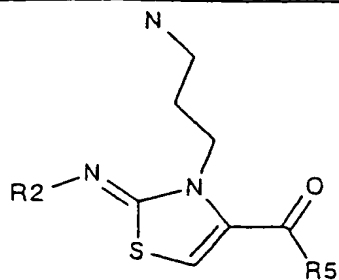
Ex.	R <sub>2</sub>	R <sub>5</sub>	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1474			82.8	5.36	491.28
1475			58.2	5.29	499.26
1476			86.5	4.37	554.27
1477			86.6	5.33	570.26
1478			84.1	5.67	574.20
1479			70.3	3.89	522.29
1480			84.2	4.94	550.28
1481			84.5	5.44	598.26
1482			86	4.84	558.24
1483			50.1	3.93	492.29
1484			82.5	5.23	503.25
1485			79.3	5.68	569.19



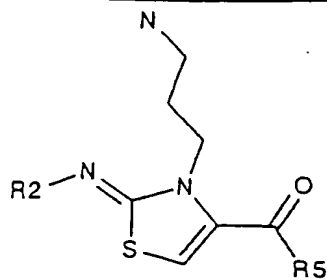
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1486			87.3	4.51	582.31
1487			79.7	5.22	465.25
1488			26.1	6.06	621.20
1489			16.1	5.51	491.28
1490			77	5.02	453.22
1491			48.4	4.88	461.16
1492			83.3	3.74	516.22
1493			84.6	4.85	532.2
1494			84.4	5.23	536.15
1495			69.9	3.29	484.23
1496			79.5	4.51	512.22
1497			81.9	4.96	560.17



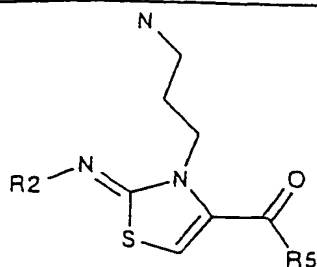
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1498			85.5	4.29	520.16
1499			67.7	3.32	454.19
1500			82.7	4.78	465.14
1501			82.1	5.26	531.13
1502			84.8	3.95	544.22
1503			77.5	4.83	427.16
1504			24	5.6	583.11
1505			17.7	5.12	453.21



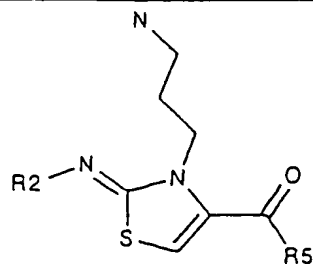
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1506			89.7	5.52	596.26
1507			87.2	5.37	562.23
1508			77	4.62	583.26
1509			89.1	3.7	579.25
1510			88.6	5.32	535.23
1511			87.6	4	570.27
1512			88	5.12	474.19
1513			90.5	5.09	519.14
1514			91.2	5.7	505.1
1515			88	3.74	475.17
1516			86.7	5.58	487.20
1517			88.3	3.88	532.18



Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1518			90.4	3	487.27
1519			92.8	4.86	443.21
1520			87.8	3.58	478.28

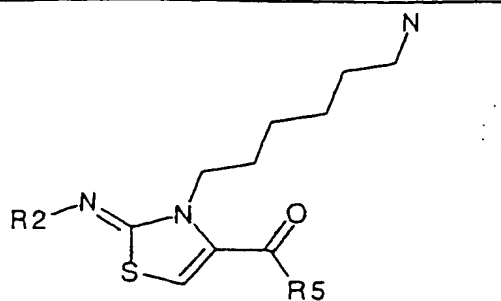


Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1521			90.4	5.2	478.28
1522			79.8	5.37	488.26
1523			90.3	5.13	523.27
1524			81.2	5.7	509.2
1525			91	3.88	479.26
1526			91.5	5.62	491.29
1527			91.1	4.1	536.28
1528			91.9	5.68	546.25
1529			92	5.54	512.24
1530			91.4	3.7	529.3
1531			92.4	5.49	485.23
1532			89.4	4.2	520.28



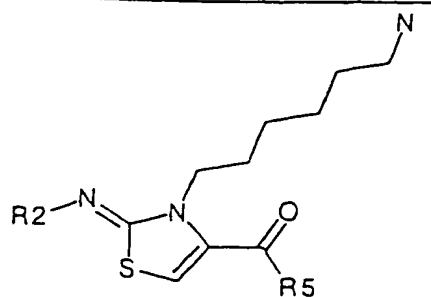
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1533			90.1	4.56	452.20
1534			76.8	4.76	462.18
1535			92.5	4.58	497.22
1536			93.4	3.21	453.21
1537			91.2	5.04	465.22
1538			92.7	3.44	510.22
1539			89.6	5.14	520.18
1540			90.2	4.93	486.17
1541			89.4	2.98	503.26
1542			90.9	4.84	459.18
1543			89.1	3.55	494.26





Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1544			83.5	4.19	425.25
1545			78.8	5.1	535.25
1546			79.7	4.67	484.23
1547			88	5.46	537.27
1548			87.4	4.72	480.22
1549			82	4.94	494.23
1550			89.6	4.92	522.18
1551			86.9	5.03	599.27
1552			84.3	4.7	486.20
1553			82.7	3.36	455.18
1554			82	3.68	543.20

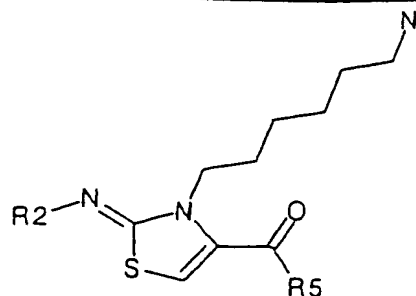
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Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1555			86.7	3.91	557.20
1556			80.9	5.06	496.26
1557			83.1	4.35	420.21
1558			87.5	5.2	530.22
1559			76.7	4.62	495.27
1560			80.9	4.44	531.25
1561			85.7	5.16	584.30
1562			85.4	4.51	527.25
1563			82.1	4.66	541.25
1564			87.4	4.66	569.19
1565			82.9	5.03	646.34

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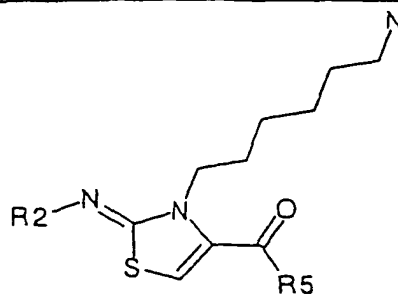
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Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1566			82.7	4.44	533.23
1567			85	3.46	502.24
1568			81.8	3.82	590.27
1569			84.5	4.03	604.26
1570			81.9	4.74	543.27
1571			84.3	4.13	467.25
1572			77.4	4.9	577.2
1573			77.7	5.15	550.3
1574			80.7	4.9	586.24
1575			86.4	5.6	639.34
1576			86.2	4.94	582.25

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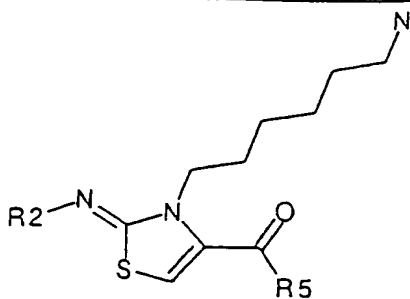
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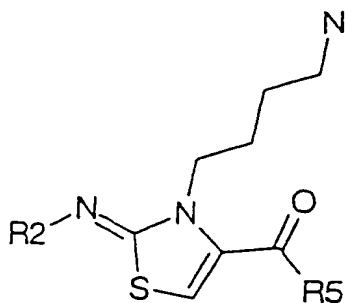
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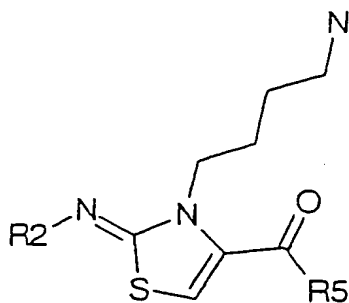
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1588			84.3	4.71	517.16
1589			89.6	5.54	570.16
1590			87.8	4.78	513.13
1591			85.2	4.99	527.15
1592			90.9	4.98	555.07
1593			88.1	5.21	632.22
1594			86.9	4.72	519.10
1595			87.4	3.47	488.12
1596			82.5	3.82	576.16
1597			86.1	4.06	590.12
1598			85.1	5.08	529.16



Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1599			84.8	4.34	453.13
1600			74.9	5.26	563.13



Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1601			88.1	3.87	409.24
1602			90.1	4.0	423.26
1603			60.2	4.1	443.21
1604			91	3.9	427.24
1605			57.6	4.4	493.23
1606			48.1	4.12	423.27
1607			45.1	4.2	443.22
1608			60.8	4.49	493.24
1609			54.5	3.98	454.26
1610			84	4.19	443.23
1611			92.8	4.49	493.25
1612			86.2	4.51	477.21



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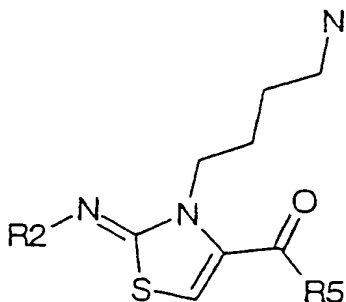
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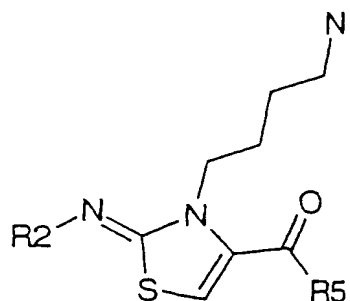
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Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1613			84.1	4.84	545.22
1614			77.7	4.34	459.30
1615			90.6	3.95	423.29
1616			91.8	4.6	499.35
1617			91.9	4.86	519.27
1618			62	4.6	545.3
1619			91.7	4.28	449.32
1620			63.1	4.62	483.29
1621			83.8	4.41	431.26
1622			64.2	4.55	445.26
1623			48.9	4.66	465.21
1624			89	4.46	449.27

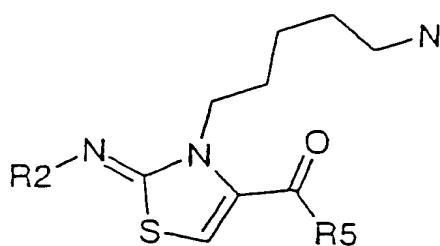




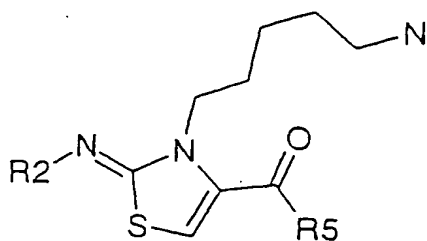
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1625			56.7	4.94	515.24
1626			78.4	4.65	445.25
1627			44.5	4.72	465.21
1628			84.7	5.01	515.24
1629			73.9	4.5	476.27
1630			76.8	4.74	465.21
1631			88.6	5.02	515.24
1632			90.6	5.05	499.19
1633			89.4	5.35	567.21
1634			80.6	4.88	481.28
1635			90.6	4.49	445.26
1636			91.1	5.14	521.28



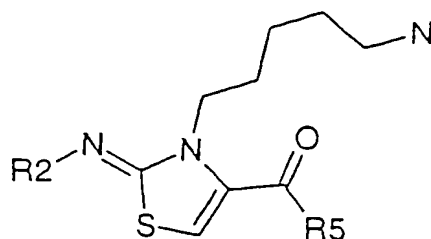
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1637			91.2	5.38	541.23
1638			90	5.1	567.3
1639			92.9	4.84	471.28
1640			88.3	5.13	505.28



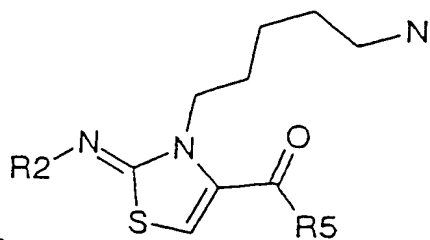
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1641			83.5	3.86	423.29
1642			81.9	4	437.30
1643			81.1	4.07	457.25
1644			89.9	3.89	441.27
1645			91.5	4.35	507.27
1646			70.6	4.08	437.31
1647			73.2	4.14	457.26
1648			91.7	4.42	507.27
1649			61.9	3.96	468.26
1650			82.6	4.16	457.25
1651			78.5	4.46	507.26
1652			80	4.46	491.21



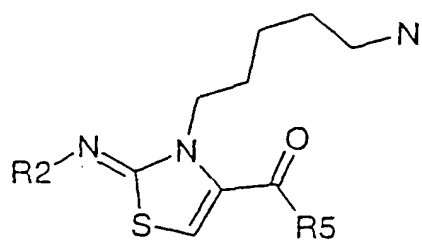
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1653			80.7	4.78	559.24
1654			90.3	4.28	473.33
1655			91.4	3.93	437.30
1656			93.5	4.55	513.33
1657			92.8	4.82	533.27
1658			58	4.5	559.3
1659			92.1	4.24	463.32
1660			92.2	4.53	497.29
1661			36.9	4.42	445.25
1662			31	4.56	459.28
1663			38.9	4.67	479.24
1664			43.4	4.47	463.27



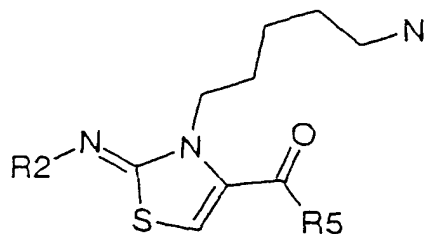
Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1665			47.9	4.98	529.2
1666			32.1	4.66	459.28
1667			23	4.74	479.23
1668			38.1	5.02	529.25
1669			35.5	4.51	490.27
1670			47.1	4.74	479.23
1671			37.1	5.04	529.25
1672			60.9	5.07	513.19
1673			82.8	5.34	581.23
1674			20.5	4.91	495.27
1675			72	4.52	459.28
1676			91.1	5.14	535.30



Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1677			89.3	5.4	555.23
1678			52	5.1	581.3
1679			91.3	4.84	485.31
1680			71.7	5.14	519.29



Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1681			72.7	4.26	471.34
1682			76.3	4.36	485.34
1683			51.6	4.47	485.33
1684			33.6	4.39	501.32
1685			79.9	4.7	539.29
1686			76	4.77	555.28
1687			53.2	4.34	489.30
1688			59.2	4.51	505.27
1689			74.7	4.57	549.21
1690			82	4.84	547.34
1691			68.8	4.49	485.32
1692			73.4	4.25	501.37



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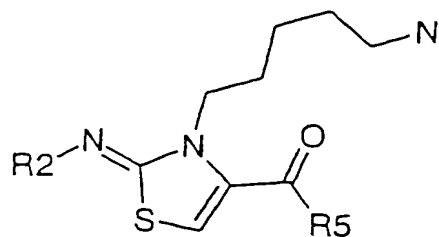
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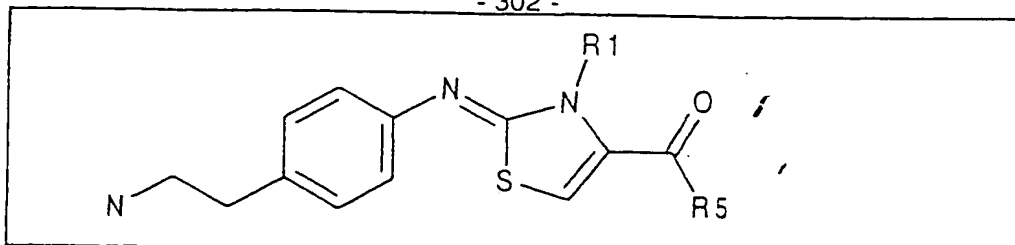
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Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1693			75.0	4.83	555.27
1694			44.5	4.39	489.30
1695			42.7	4.57	505.25
1696			79.8	4.97	547.32
1697			78.9	4.56	499.39
1698			70.8	4.27	531.36
1699			77.5	4.35	507.33
1700			78.9	4.34	507.33
1701			75.8	4.27	507.32
1702			74.9	4.41	507.32
1703			75.3	4.49	507.29
1704			73.5	4.75	539.22





Ex.	R2	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1705			82.9	4.7	521.31



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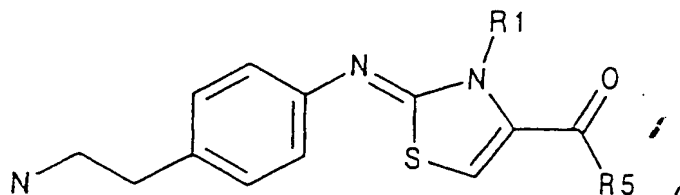
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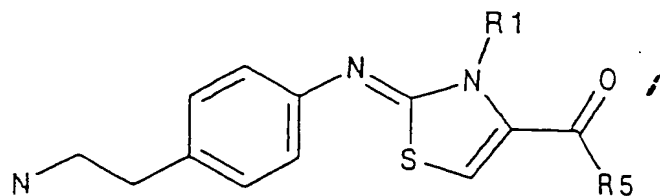
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1706			87.3	3.8	448.31
1707			86.0	4.3	482.24
1708			90.0	2.4	370.24
1709			76.6	3.88	387.26
1710			53.2	3.0	394.2
1711			91.2	2.3	449.29
1712			87.7	4.13	443.29
1713			88.3	3.7	419.28
1714			70.8	3.5	437.25
1715			87.0	4.4	469.30
1716			82.5	4.12	485.20
1717			88.1	2.59	428.29



Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1718			88.7	2.8	490.35
1719			79.0	4.68	529.23
1720			78.0	3.94	399.29
1721			87.4	3.7	480.32
1722			83.1	4.14	514.28
1723			89.1	2.44	402.24
1724			81.5	3.73	419.3
1725			56.1	3.0	416.2
1726			90.1	2.3	481.33
1727			87.3	3.96	475.31
1728			75.2	2.9	448.3
1729			85.7	3.61	451.29



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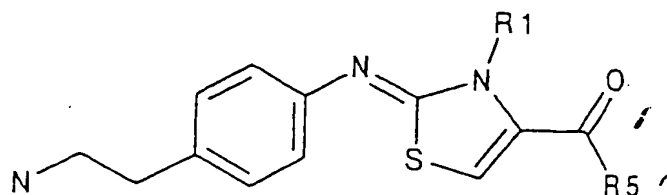
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1730			74.5	3.37	469.28
1731			83.7	4.22	501.32
1732			86.7	3.95	517.20
1733			80.6	2.61	460.32
1734			80.8	2.8	522.35
1735			74.0	4.48	561.23
1736			81.2	3.8	431.31
1737			87.1	4.76	546.27
1738			85.5	5.16	580.24
1739			85.5	3.72	468.24
1740			82.1	4.74	485.29
1741			80.7	3.04	492.24



Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1742			87.7	3.4	547.28
1743			81.9	4.96	541.23
1744			55.2	2.9	514.27
1745			87.2	4.7	517.25
1746			73.7	4.39	535.21
1747			84.3	5.22	567.25
1748			74.7	4.9	583.16
1749			76.8	3.53	526.28
1750			84.3	3.7	588.34
1751			74.4	5.41	627.20
1752			80.9	4.88	497.31
1753			83.4	4.53	516.2

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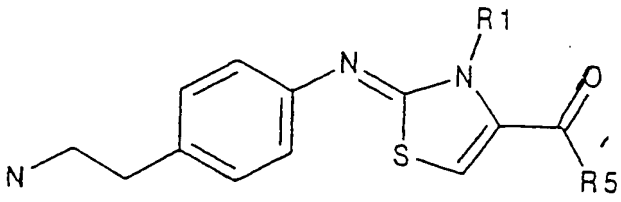
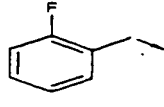
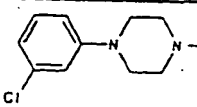
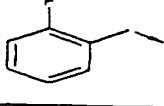
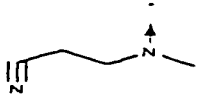
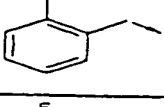
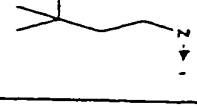
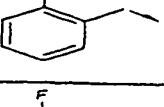
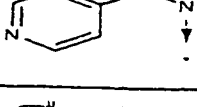
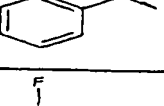
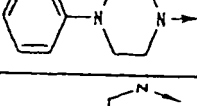
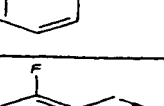
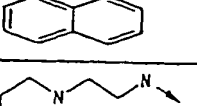
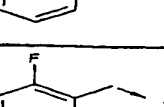
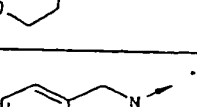
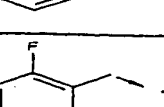
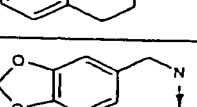
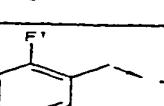
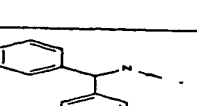
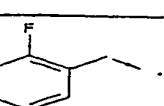
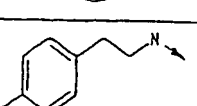
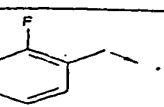
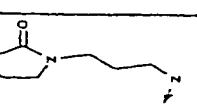


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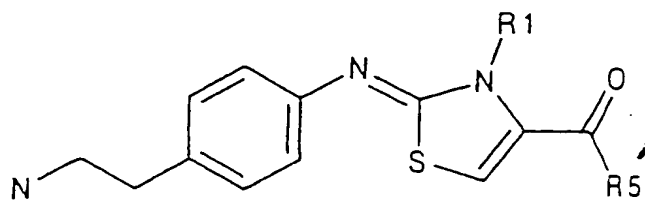
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1754			83.2	4.96	550.24
1755			84.1	3.39	438.25
1756			84.7	4.71	455.28
1757			56.6	2.8	462.24
1758			85.0	3.0	517.30
1759			84.6	4.9	511.26
1760			82.1	2.8	484.3
1761			84.4	4.44	487.27
1762			52.0	4.3	505.23
1763			84.5	5.12	537.28
1764			81.5	4.93	553.17
1765			80.2	3.34	496.29



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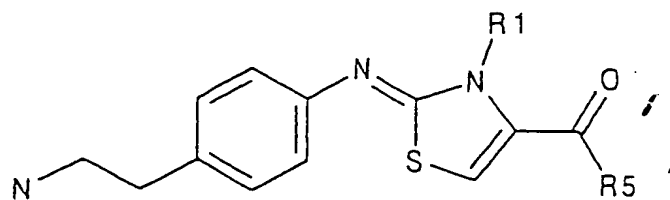
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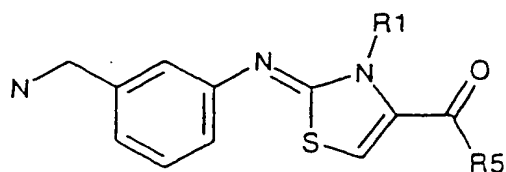
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1766			85.9	3.5	558.31
1767			53.4	5.39	597.22
1768			81.6	4.81	467.29
1769			83.5	3.5	540.32
1770			82.4	5.01	574.27
1771			80.9	3.72	462.30
1772			77.9	4.78	479.36
1773			79.3	3.11	486.32
1774			85.0	3.4	541.35
1775			85.3	4.9	535.31
1776			74.9	3.0	508.34
1777			83.9	4.58	511.33



Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1778			69.1	4.4	529.3
1779			83.1	5.1	561.3
1780			81.8	4.9	577.23
1781			83.6	3.64	520.34
1782			80.9	3.7	582.4
1783			68.0	5.34	621.28
1784			76.3	4.85	491.36





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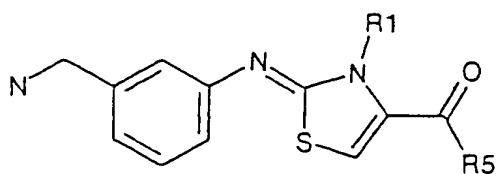
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1785			77.9	4.44	435.25
1786			78.8	4.83	437.30
1787			79.5	3.13	464.27
1788			80.3	3.28	526.38
1789			86.6	4.67	543.32
1790			74.8	2.9	458.32
1791			81.7	3.99	508.34
1792			86.9	5.41	526.38
1793			86.4	4.85	511.27
1794			82.2	5.07	533.35
1795			83.1	3.55	536.28
1796			82.3	4.66	471.3



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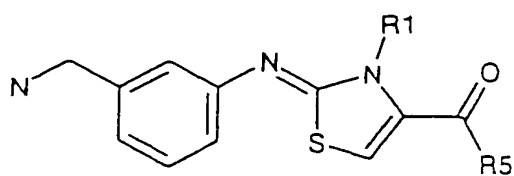
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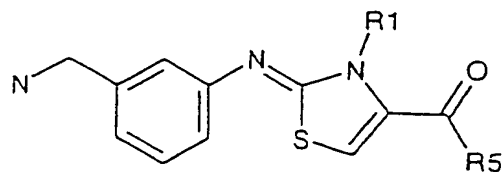
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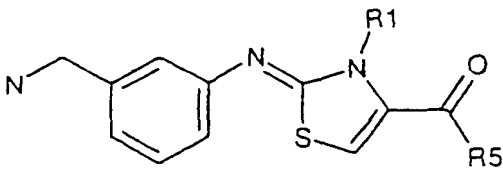
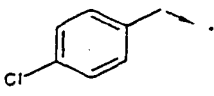
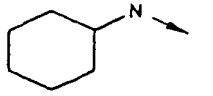
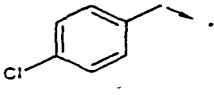
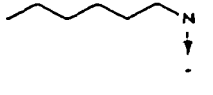
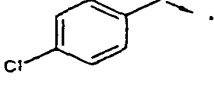
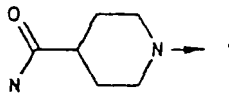
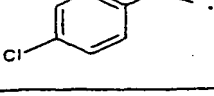
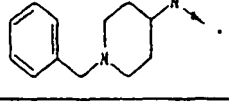
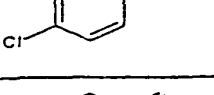
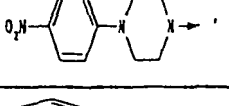
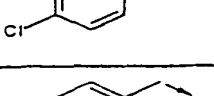
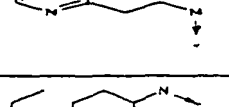
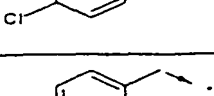
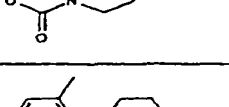
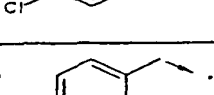

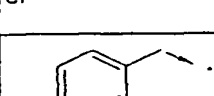
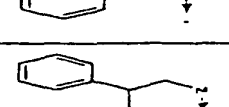
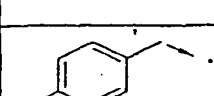
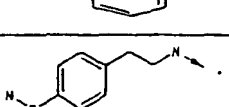
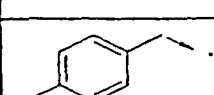
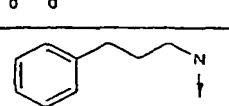
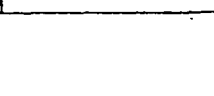

Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1797			86.3	4.41	461.31
1798			85.1	4.95	505.33
1799			76.0	3.5	532.3
1800			81.1	4.87	483.34
1801			68.62	3.96	387.33
1802			73.4	4.39	389.33
1803			81.2	2.57	416.32
1804			79.2	2.9	478.3
1805			83.2	4.26	495.34
1806			70.2	2.5	410.3
1807			73.3	3.6	460.37
1808			75.0	5.01	478.39

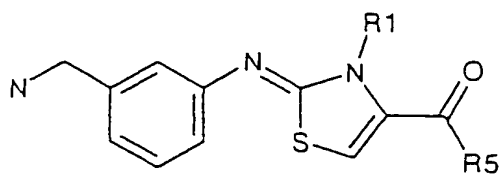


Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1809			70.3	4.45	463.31
1810			83.9	4.73	485.37
1811			76.5	3.14	488.31
1812			79.1	4.28	423.35
1813			79.2	3.99	413.29
1814			75.5	4.55	457.33
1815			67.7	3.1	484.3
1816			62.7	4.44	435.33
1817			85.7	5.02	471.33
1818			70.2	5.31	473.37
1819			86.6	3.59	500.35
1820			83.8	3.7	562.4



Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1821			88.5	5.04	579.32
1822			39.8	3.3	494.3
1823			85.8	4.55	544.33
1824			86.4	5.78	562.36
1825			84.3	5.27	547.25
1826			69.7	5.58	569.32
1827			70.3	4.17	572.27
1828			85.4	5.17	507.34
1829			82.3	4.91	497.28
1830			82.4	5.41	541.29
1831			79.4	3.8	568.3
1832			86.9	5.31	519.33

					
Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1833			86.3	4.99	455.27
1834			84.5	5.3	457.30
1835			88.3	3.42	484.27
1836			83.6	3.65	546.29
1837			88.8	4.91	563.24
1838			65.2	3.3	478.24
1839			87.6	4.5	528.30
1840			90.4	5.68	546.30
1841			82.8	5.31	531.23
1842			68.2	5.57	553.28
1843			72.4	4.11	556.21
1844			83.9	5.15	491.29



Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1845			86.4	4.93	481.27
1846			86.3	5.29	525.25
1847			82.6	3.7	552.3
1848			88.1	5.3	503.29
1849			82.9	4.25	451.32
1850			82.1	4.64	453.35
1851			85.6	2.72	480.33
1852			82.9	3.16	542.35
1853			87.7	4.28	559.29
1854			75.3	2.82	474.33
1855			84.4	3.83	524.32
1856			87.0	5.0	542.36

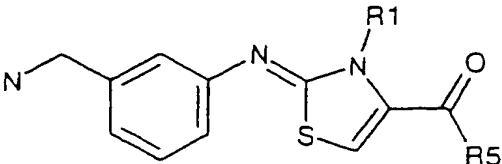
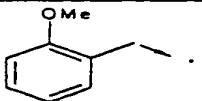
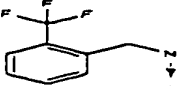
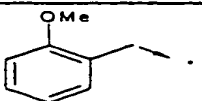
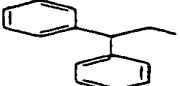
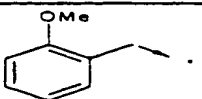
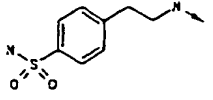
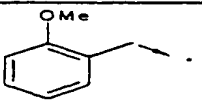
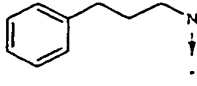
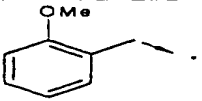
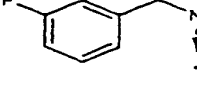
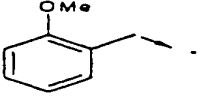
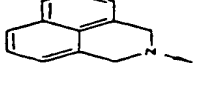
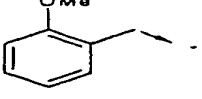
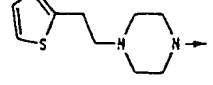
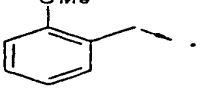
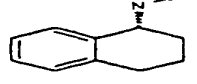
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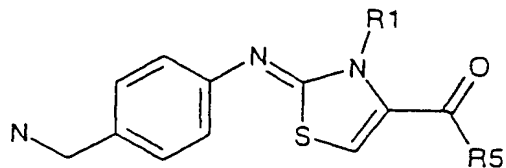
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1857			82.6	4.73	527.28
1858			65.8	5.01	549.31
1859			76.4	3.49	552.26
1860			80.4	4.54	487.35
1861			81.3	4.28	477.30
1862			79.9	4.59	521.29
1863			77.5	3.2	548.3
1864			86.5	4.65	499.32



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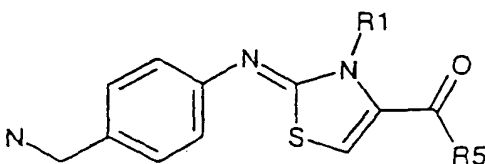
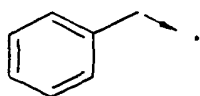
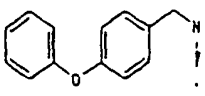
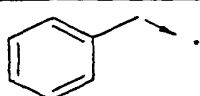

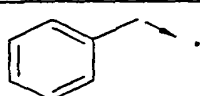
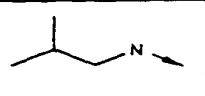
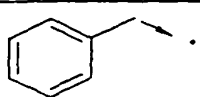
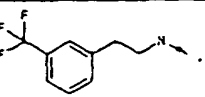
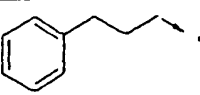
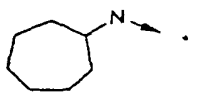
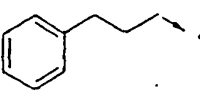
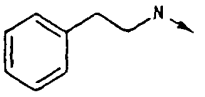
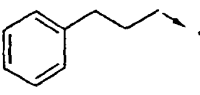
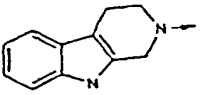
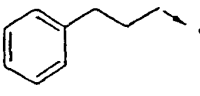
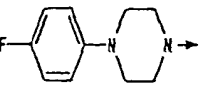
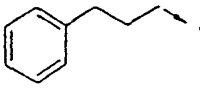

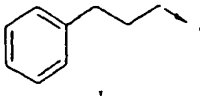
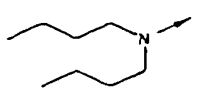
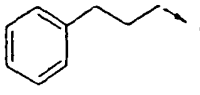
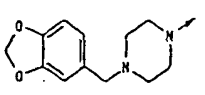
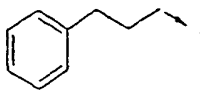

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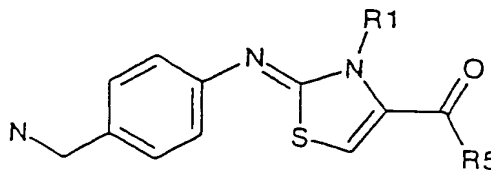
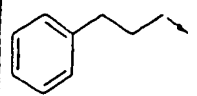
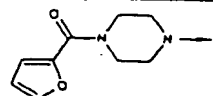
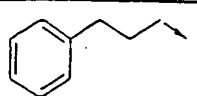
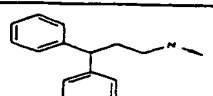
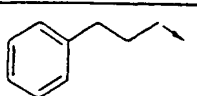
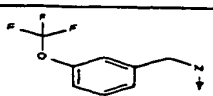
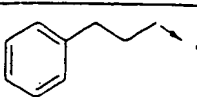
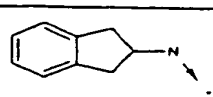
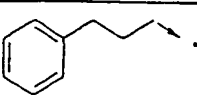
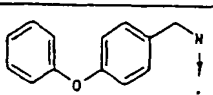
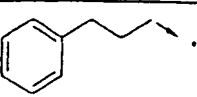
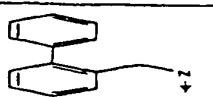
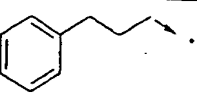
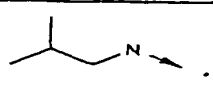
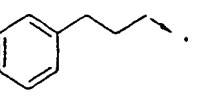
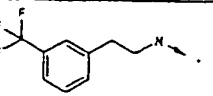
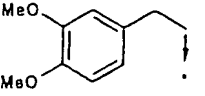
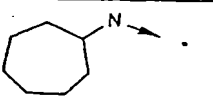
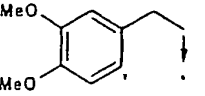
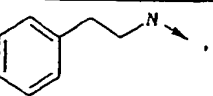
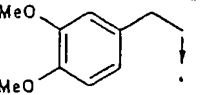
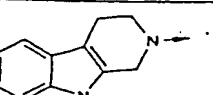
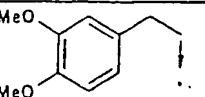
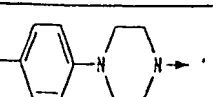
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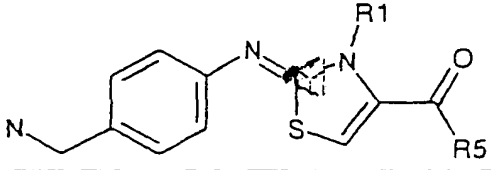
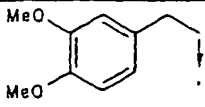
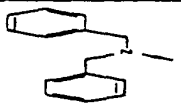
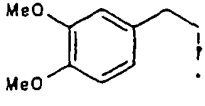
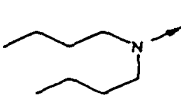
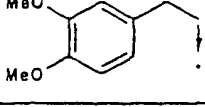
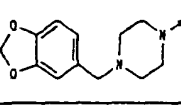
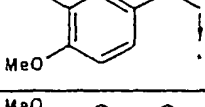
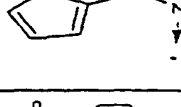
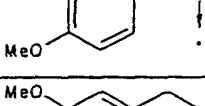

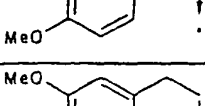
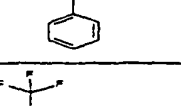
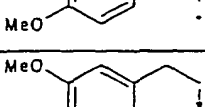
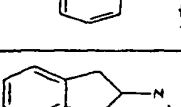
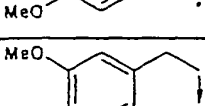
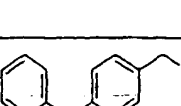
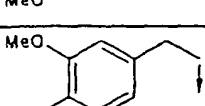

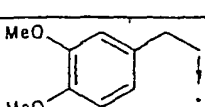
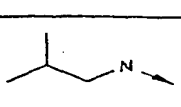
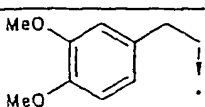
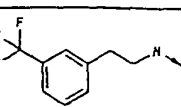


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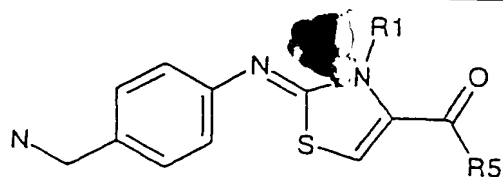
Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1865			84.7	4.94	435.29
1866			85.0	4.66	443.26
1867			26.2	4.82	494.26
1868			88.4	4.8	502.28
1869			83.6	5.48	519.28
1870			63.17	5.3	451.33
1871			91.1	3.4	542.3
1872			35.7	4.48	435.20
1873			88.8	3.8	502.26
1874			87.1	5.41	533.29
1875			89.5	5.14	513.22
1876			47.8	4.82	455.24



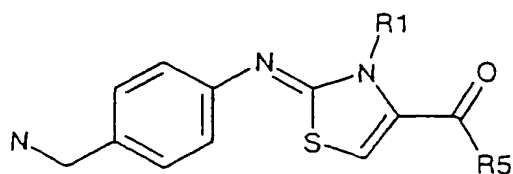
					
Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1877			77.1	5.32	521.24
1878			81.8	5.31	505.26
1879			19.7	4.37	395.24
1880			61.4	5.14	511.22
1881			82.7	4.95	463.31
1882			82.2	4.71	471.27
1883			67.2	4.84	522.26
1884			87.7	4.9	530.28
1885			79.4	5.54	547.28
1886			80.8	5.3	479.34
1887			88.9	3.6	570.24
1888			30.2	4.53	463.23

					
Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1889			88.9	3.98	530.26
1890			84.2	5.42	561.30
1891			75.8	5.17	541.22
1892			85.8	4.86	483.28
1893			71.7	5.33	549.26
1894			86.6	5.34	533.29
1895			54.1	4.43	423.28
1896			47.7	5.16	539.26
1897			74.6	4.44	509.30
1898			77.6	4.2	517.27
1899			38.8	4.53	568.26
1900			80.1	4.5	576.3

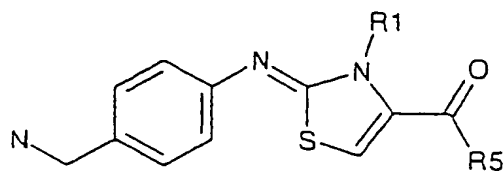
					
Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
5					
1901			72.3	5.17	593.30
10					
1902			77.0	4.88	525.34
1903			80.5	3.3	616.3
15					
1904			34.6	4.03	509.21
1905			81.3	3.6	576.2
20					
1906			77.1	5.04	607.31
1907			79.6	4.76	587.24
25					
1908			77.8	4.38	529.28
1909			78.0	4.95	595.28
30					
1910			81.1	4.88	579.29
1911			32.4	3.89	469.29
35					
1912			49.3	4.7	585.26



	Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
5	1913			87.0	5.59	503.20
10	1914			88.5	5.3	511.15
	1915			69.5	5.28	562.16
15	1916			89.4	5.3	570.1
	1917			79.1	5.98	587.17
20	1918			82.4	5.84	519.23
	1919			89.5	3.9	610.1
25	1920			27.2	5.12	503.11
	1921			88.6	4.41	570.13
30	1922			86.4	5.91	601.19
	1923			84.9	5.66	581.11
35	1924			86.4	5.44	523.13



Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1925			61.9	5.81	589.16
1926			84.7	5.85	573.15
1927			36.8	5.1	463.16
1928			76.4	5.68	579.13
1929			79.4	4.65	415.30
1930			84.5	4.41	423.29
1931			44.0	4.62	474.29
1932			86.1	4.65	482.3
1933			78.5	5.33	499.31
1934			79.6	5.06	431.33
1935			84.6	3.4	522.30
1936			54.6	4.2	415.21



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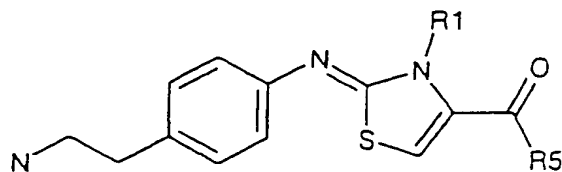
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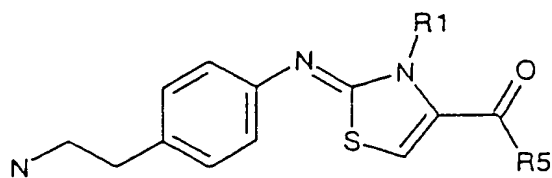
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1937			85.4	3.7	482.29
1938			83.5	5.21	513.32
1939			85.7	4.92	493.24
1940			83.0	4.58	435.29
1941			75.1	5.1	501.31
1942			88.2	5.1	485.31
1943			76.1	4.08	375.28
1944			81.1	4.9	491.28



Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1945			84.3	4.24	512.26
1946			85.4	3.63	514.25
1947			86.8	3.1	526.27
1948			87.7	4.32	530.23
1949			87.5	4.24	557.23
1950			88.8	2.9	513.26
1951			84.5	4.92	540.28
1952			87.7	4.49	526.27
1953			62.5	3.66	567.26
1954			89	4.08	542.26
1955			87.7	4.38	530.24
1956			82.4	2.7	513.28



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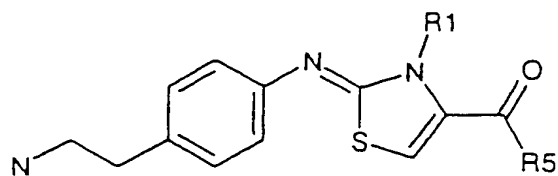
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1957			87.7	4.31	557.23
1958			91.0	4.44	556.27
1959			80.7	3.44	514.25
1960			68.6	4.67	535.24
1961			85.3	4.32	526.27
1962			83.0	3.75	528.25
1963			88.7	3.28	540.28
1964			86.8	4.37	544.25
1965			89.4	4.29	571.24
1966			86.9	3.1	527.25
1967			86.1	4.94	554.29
1968			87.6	4.54	540.27





5

Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1969			65.4	3.76	581.27
1970			86.3	4.16	556.28
1971			86.0	4.43	544.25
1972			83.2	2.8	527.3
1973			84.8	4.38	571.24
1974			87.8	4.5	570.28
1975			80.9	3.55	528.26
1976			62.7	4.71	549.27
1977			85.7	4.41	526.29
1978			84.2	3.82	528.27
1979			87.4	3.28	540.28
1980			86.6	4.47	544.24

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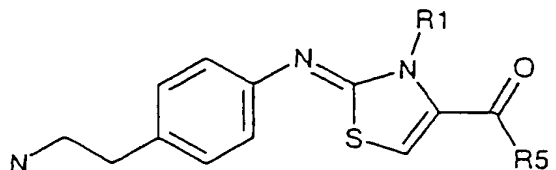
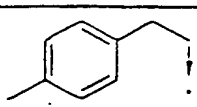
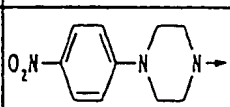
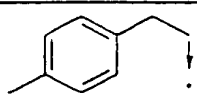
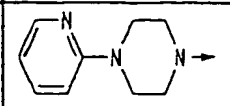
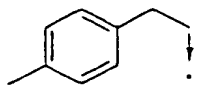
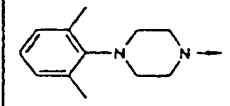
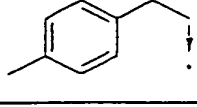
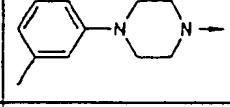
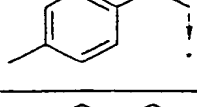
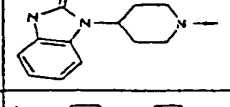
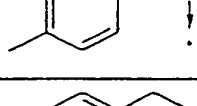
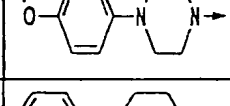
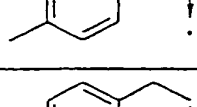
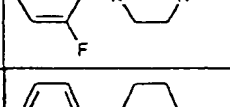
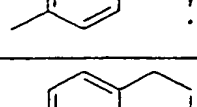
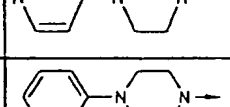
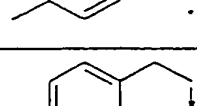
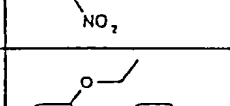
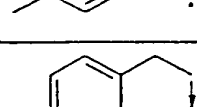
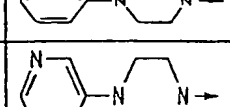
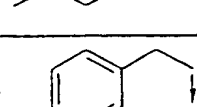
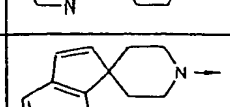
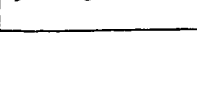
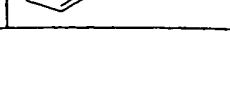
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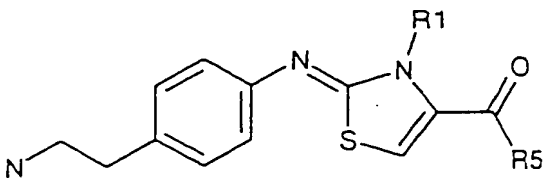
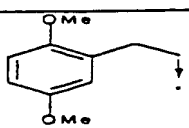
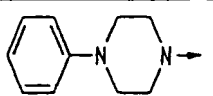
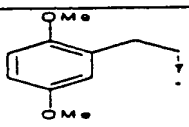
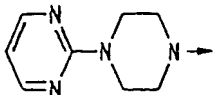
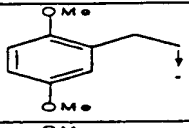
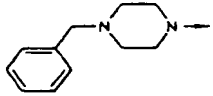
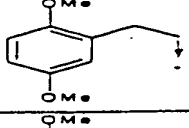
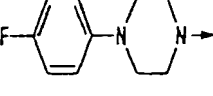
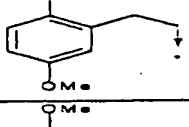
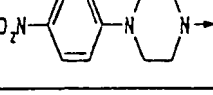
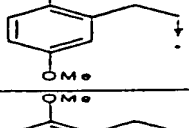
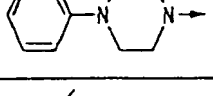
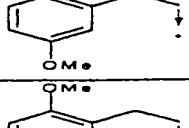
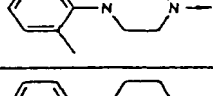
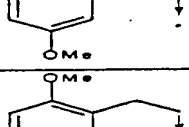
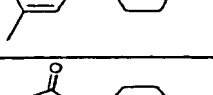
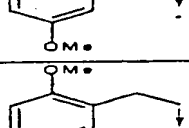

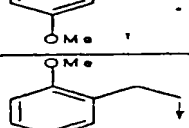
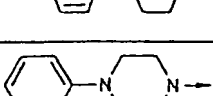
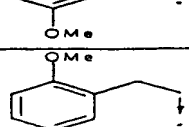
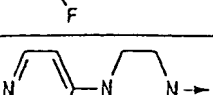
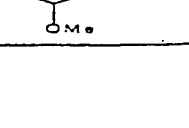
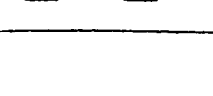
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1981			86.4	4.38	571.24
1982			85.9	3.1	527.27
1983			85.3	5.06	554.28
1984			85.3	4.66	540.28
1985			60.8	3.8	581.28
1986			86.1	4.25	556.28
1987			86.4	4.54	544.25
1988			75.9	2.86	527.28
1989			86.5	4.46	571.24
1990			88.4	4.6	570.29
1991			79.8	3.62	528.27
1992			63.2	4.82	549.26

					
Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
1993			81.8	4.15	572.25
1994			81.0	3.58	574.25
1995			83.5	3.08	586.3
1996			84.3	4.2	590.27
1997			85.3	4.12	617.26
1998			86.1	2.91	573.28
1999			85.5	4.74	600.31
2000			87.3	4.37	586.28
2001			68.4	3.6	627.28
2002			85.4	3.98	602.28
2003			83.1	4.26	590.27
2004			84.5	2.7	573.26

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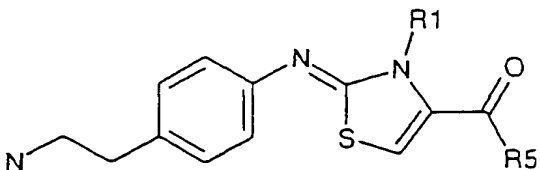
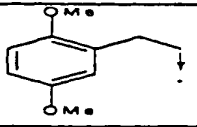
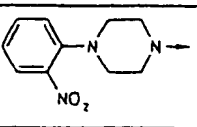
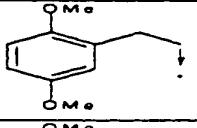
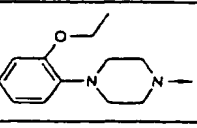
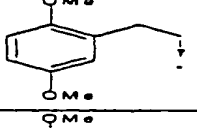
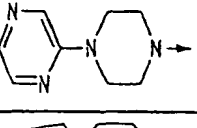
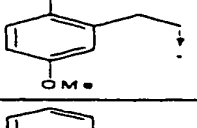
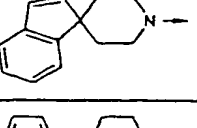
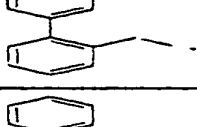
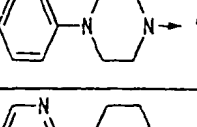
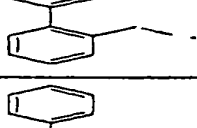
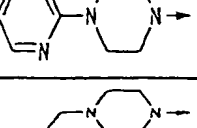
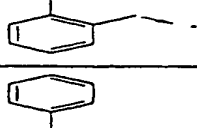
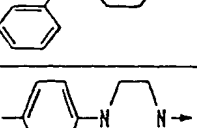

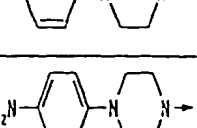
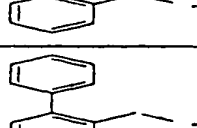
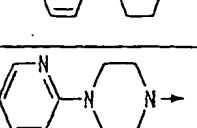
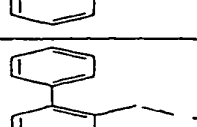
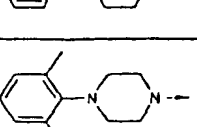
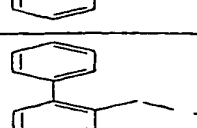
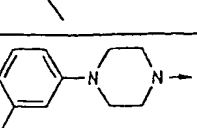
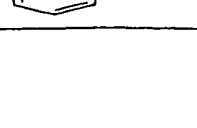
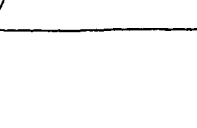
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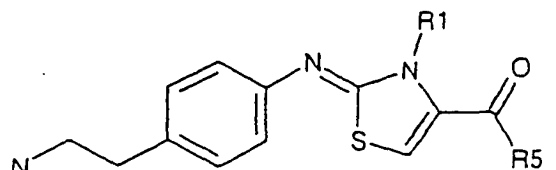
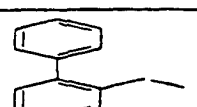
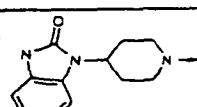

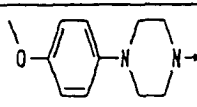
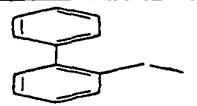
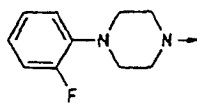
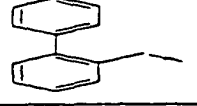
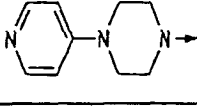
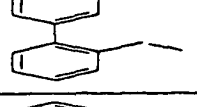
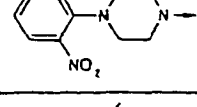
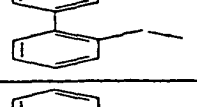
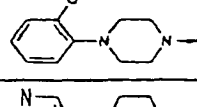
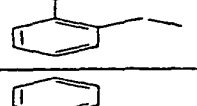
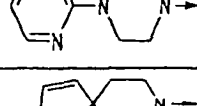
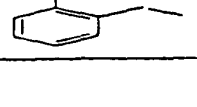
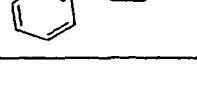
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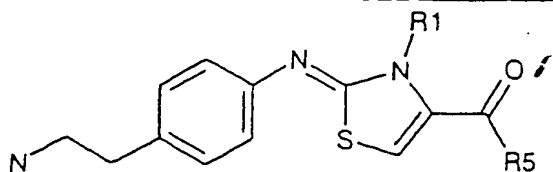
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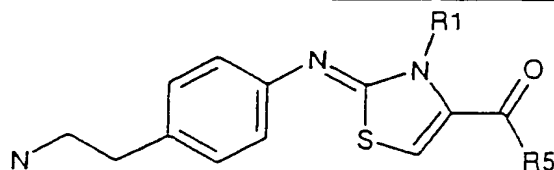
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2005			85.9	4.2	617.27
2006			86.9	4.32	616.31
2007			81.2	3.4	574.24
2008			69.0	4.54	595.29
2009			82.1	4.72	574.25
2010			80.1	4.15	576.27
2011			83.9	3.53	588.27
2012			80.8	4.78	592.26
2013			83.0	4.68	619.26
2014			85.6	3.35	575.25
2015			82.9	5.41	602.30
2016			81.9	4.96	588.26

					
Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2017			58.6	4.09	629.29
2018			81.7	4.53	604.27
2019			81.4	4.84	592.26
2020			78.7	3.06	575.31
2021			83.9	4.74	619.25
2022			82.6	4.89	618.29
2023			79.5	3.9	576.27
2024			64.2	5.15	597.27



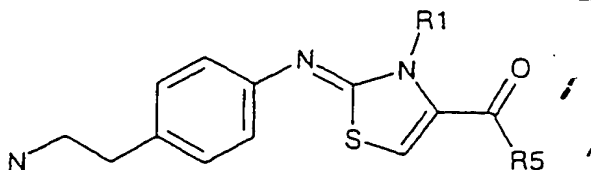
Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2025			88.8	4.94	574.23
2026			88.4	4.96	592.25
2027			87.7	4.86	619.24
2028			89.7	3.61	575.2
2029			70.4	5.13	571.25
2030			88.0	5.58	602.28
2031			87.8	5.15	588.26
2032			76.5	4.24	629.28
2033			88.8	4.7	604.27
2034			88.3	5.04	592.25
2035			89.5	4.96	619.24
2036			87.5	5.41	642.26



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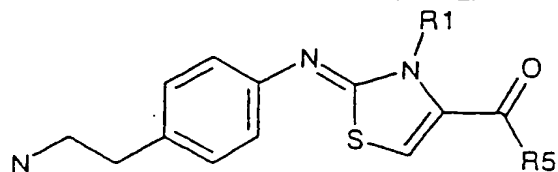
Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2037			88.9	5.12	610.24
2038			89.4	5.07	618.27
2039			88.7	5.42	687.24
2040			87.7	3.68	580.30
2041			85.2	4.89	574.23
2042			84.4	4.9	592.25
2043			84.7	4.78	619.23
2044			89.0	3.58	575.25
2045			61.5	5.16	571.22
2046			83.2	5.57	602.28
2047			84.4	5.1	588.25
2048			73.2	4.25	629.27

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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2049			85.5	4.64	604.26
2050			85.6	4.99	592.2
2051			85.7	4.93	619.24
2052			86.2	5.34	642.25
2053			85.1	5.06	610.23
2054			84.6	5.06	618.27
2055			85.4	5.37	687.23
2056			85.8	3.68	580.30
2057			68.0	4.37	528.26
2058			86.3	4.41	546.22
2059			88.1	4.32	573.19
2060			86.1	3	529.25





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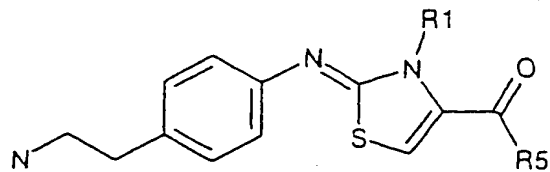
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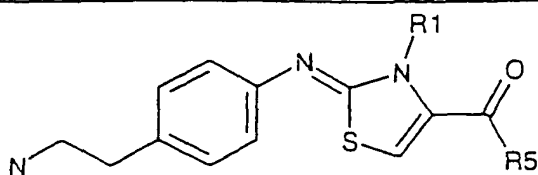
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2061			67.2	4.56	525.25
2062			91.2	4.98	556.26
2063			87.8	4.56	542.26
2064			75.6	3.73	583.23
2065			88.7	4.16	558.23
2066			88.4	4.46	546.22
2067			87.4	4.4	573.20
2068			87.7	4.88	596.21
2069			87.9	4.56	564.21
2070			87.5	4.51	572.26
2071			88.8	4.91	641.20
2072			86.2	3.08	534.27



Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2073			71.7	4.78	562.25
2074			82.1	4.8	580.23
2075			82.6	4.68	607.23
2076			79.5	3.4	563.21
2077			67.5	4.92	559.23
2078			83.0	5.39	590.27
2079			82.5	4.98	576.26
2080			42.5	4.1	617.23
2081			86.9	4.58	592.26
2082			82.5	4.88	580.23
2083			81.4	4.77	607.23
2084			82.3	5.24	630.26



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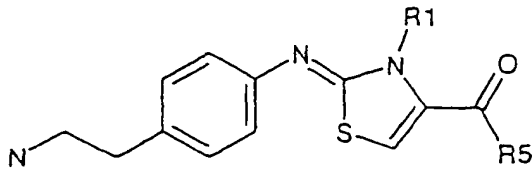
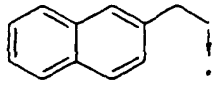
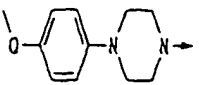
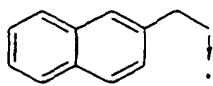
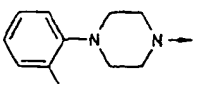
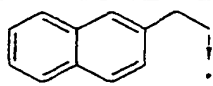
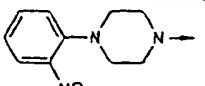
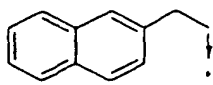
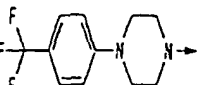
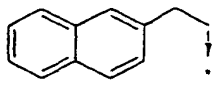
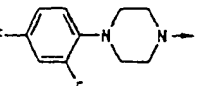
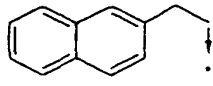
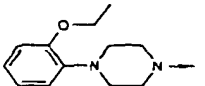
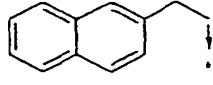
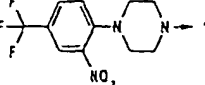
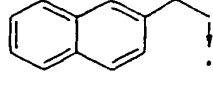
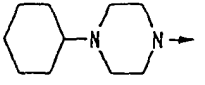
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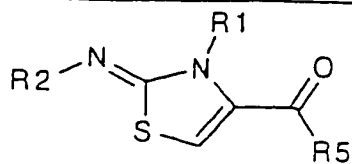
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Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2085			83.5	4.97	598.20
2086			81.6	4.93	606.28
2087			82.7	5.25	675.23
2088			84.4	3.4	568.26
2089			67.0	4.64	562.24
2090			83.0	4.66	580.23
2091			83.6	4.54	607.22
2092			82.5	3.3	563.25
2093			84.2	4.8	559.22
2094			86.2	5.21	590.29
2095			83.2	4.82	576.28
2096			62.8	3.99	617.26

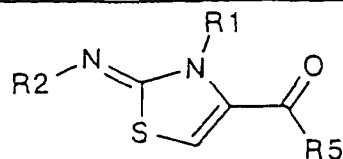
					
Ex.	R1	R5	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2097			86.0	4.44	592.2
2098			85.8	4.72	580.25
2099			84.0	4.62	607.23
2100			83.4	5.09	630.26
2101			84.8	4.8	598.21
2102			83.7	4.78	606.29
2103			83.6	5.1	675.24
2104			5.6	3.05	568.28



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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2105				81.5	4.9	468.27
2106				81.4	5.01	465.28
2107				77.3	5.34	505.31
2108				73.5	4.7	447.29
2109				70.5	5.28	499.26
2110				73.9	5.38	491.30
2111				72.0	4.5	489.31
2112				73.0	5.5	521.29
2113				90.0	4.23	381.29
2114				76.1	5.02	443.30
2115				56.9	4.2	434.32
2116				79.8	4.29	431.31
2117				79.1	4.45	471.35
2118				70.2	3.56	413.29

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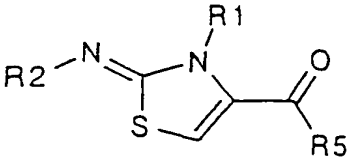
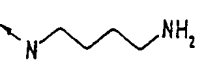
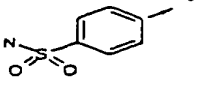
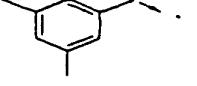
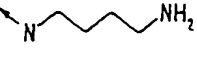
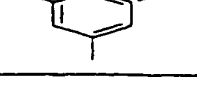
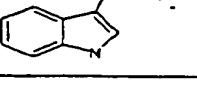
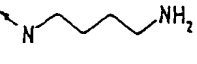
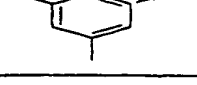
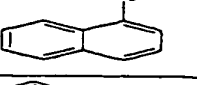
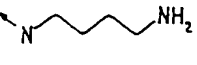
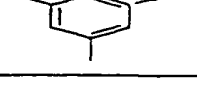
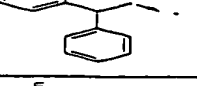
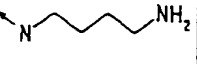
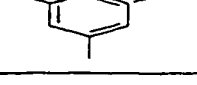

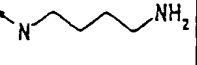
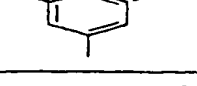
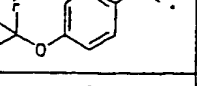
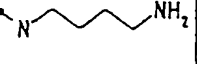
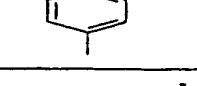
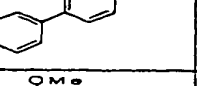
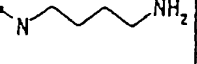
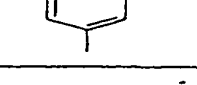

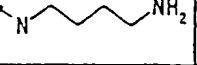
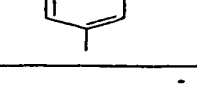
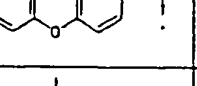
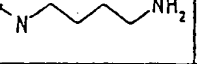
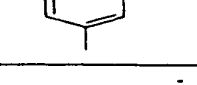

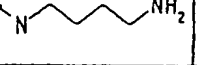
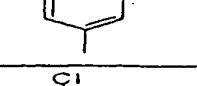
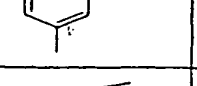
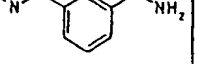
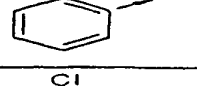
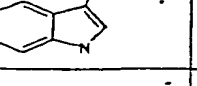
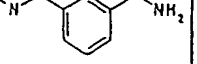
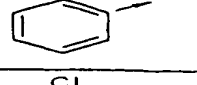
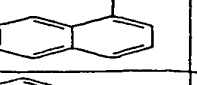
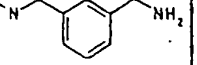
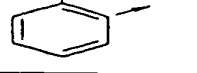
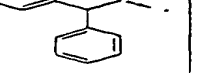
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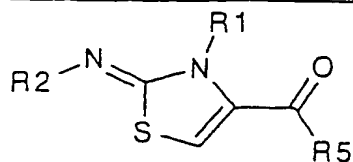
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2119				72.4	4.68	465.27
2120				78.3	4.66	457.33
2121				90.1	3.41	455.33
2122				82.2	4.38	487.36
2123				68.8	2.99	347.34
2124				75.2	4.13	409.33
2125				56.9	4.01	513.30
2126				70.1	3.88	510.29
2127				77.8	4.16	550.29
2128				67.7	3.49	492.28
2129				71	4.27	536.28
2130				71.4	3.38	534.30
2131				67.7	4.29	566.30
2132				54.5	2.98	426.29

						
Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2133				70.1	3.85	488.31
2134				57.1	4.5	462.36
2135				83.2	4.61	459.35
2136				91.6	4.72	499.40
2137				80.7	3.94	441.32
2138				73.9	4.99	493.32
2139				77.5	4.95	485.37
2140				77.4	3.79	483.36
2141				66.1	4.62	515.38
2142				70.1	3.49	375.33
2143				74.1	4.46	437.35
2144				93.8	5.14	516.28
2145				90.0	5.27	513.28
2146				81.4	5.58	553.30



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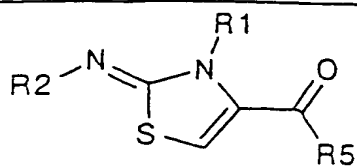
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2147				78.6	5.02	495.27
2148				81.4	5.51	547.21
2149				85.5	5.62	539.29
2150				78.9	4.86	537.28
2151				83.2	5.76	569.28
2152				90.5	4.62	429.28
2153				91.8	5.31	491.31
2154				60.4	4.47	482.33
2155				83.6	4.62	479.31
2156				79.1	4.72	519.34
2157				72.6	3.96	461.31
2158				75.7	5.0	513.27
2159				79.3	4.99	505.34
2160				89.6	3.72	503.34





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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2161				89.6	4.7	535.32
2162				73.5	3.38	395.32
2163				80.1	4.5	457.32
2164				58.8	4.24	561.29
2165				77.9	4.16	558.27
2166				85.5	4.42	598.29
2167				82.8	3.87	540.27
2168				1.54	4.52	592.25
2169				56.0	4.54	584.25
2170				82.5	3.76	582.30
2171				71.8	4.58	614.31
2172				71.9	3.43	474.30
2173				80.9	4.16	536.28
2174				61.9	4.76	510.36

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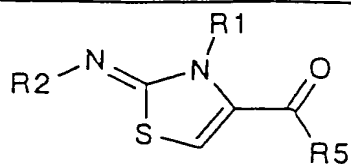
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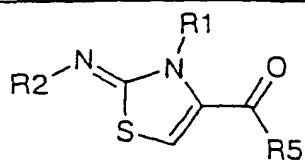
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2175				83.1	4.93	507.35
2176				92.0	4.99	547.36
2177				88.3	4.27	489.35
2178				86.3	5.41	541.29
2179				79.7	5.36	533.36
2180				82.5	4.13	531.35
2181				74.0	4.99	563.34
2182				76	3.89	423.35
2183				79.8	4.89	485.38



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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2184				80.8	4.43	501.32
2185				66.2	4.18	545.31
2186				64.6	5.18	569.27
2187				57.2	4.78	589.30
2188				65.7	4.41	529.36
2189				65.4	4.52	549.28
2190				65.8	4.24	521.29
2191				71.4	4.19	481.37
2192				83.9	4.8	577.32
2193				76.5	4.54	583.24
2194				67.2	4.76	473.22
2195				66.6	4.69	517.20
2196				71	5.2	541.18
2197				69	4.73	561.15

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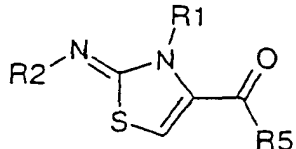
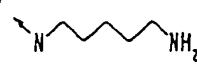
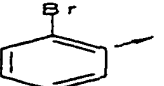
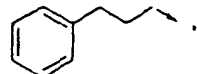
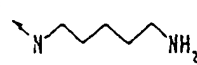
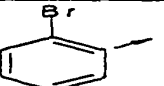
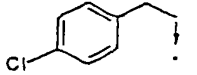
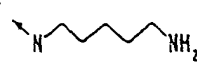
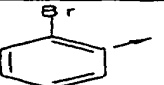
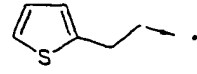
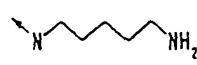
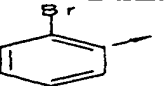

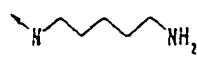
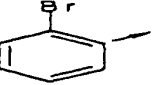
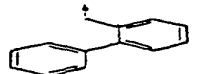
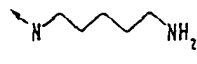
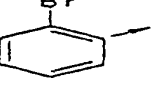
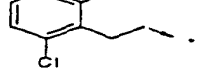
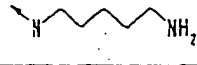
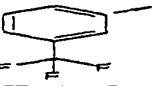
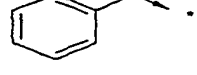
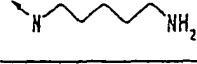
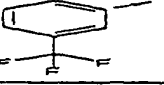
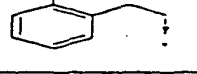
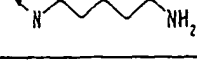
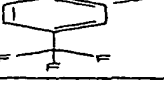
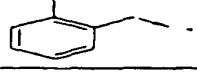
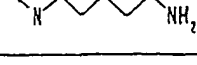
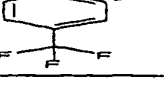
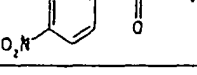
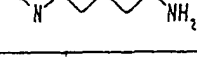
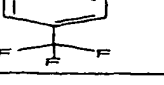

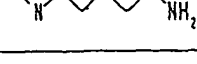



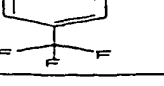
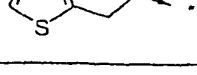

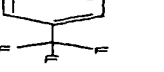

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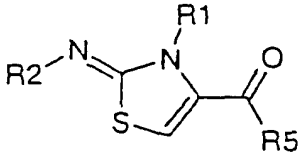
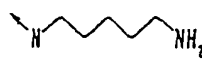
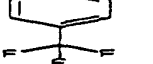
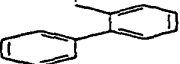
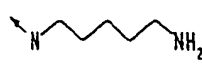
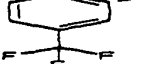
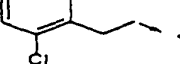
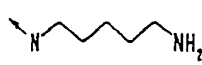
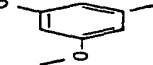
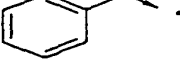
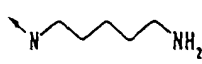
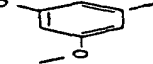
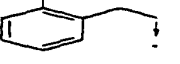
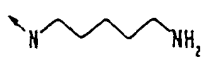
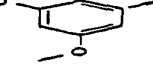
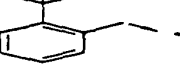
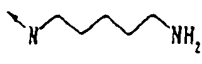
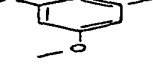

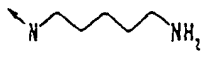


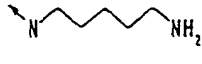
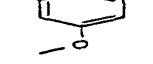

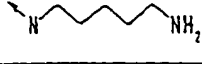
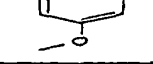

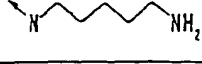
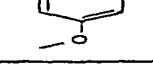

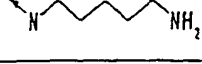
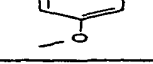
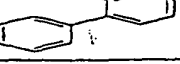
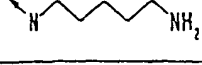
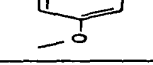
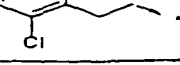

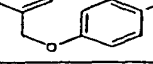
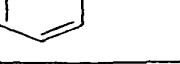
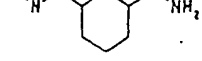
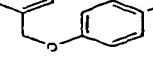
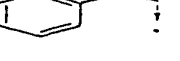
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2198				74.8	5.04	501.24
2199				69.5	5.18	521.16
2200				79.3	4.8	493.18
2201				74.9	4.79	453.24
2202				68.9	5.41	549.20
2203				68	5.2	555.11
2204				66	5.02	463.27
2205				62.2	4.83	507.28
2206				65.2	5.48	531.24
2207				66.3	4.99	551.22
2208				72.9	5.22	491.31
2209				77.2	5.31	511.24
2210				62.8	4.98	483.24
2211				62.4	4.98	443.31

						
Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2212				69.6	5.55	539.29
2213				63.5	5.41	545.19
2214				41.2	4.09	455.28
2215				58.5	3.73	499.35
2216				68.8	4.78	523.28
2217				36.2	4.37	543.28
2218				42.9	4.1	483.36
2219				46.1	4.24	503.30
2220				48.4	3.87	475.28
2221				39	3.8	435.34
2222				48.3	4.55	531.30
2223				47	4.33	537.20
2224				57.4	4.64	541.34
2225				69.1	4.34	585.37

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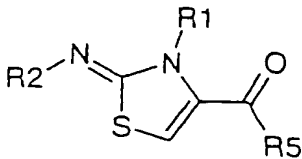
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2226				64.6	5.36	609.35
2227				40.2	4.94	629.34
2228				62.6	4.57	569.3
2229				68	4.72	589.31
2230				61.2	4.44	561.31
2231				61.2	4.37	521.36
2232				80.7	5.02	617.37
2233				74.2	4.77	623.28
2234				68.1	4.99	513.23
2235				66.1	4.98	557.22
2236				68.8	5.38	581.20
2237				69.7	4.9	601.19
2238				67.1	5.27	541.23
2239				72.6	5.45	561.16

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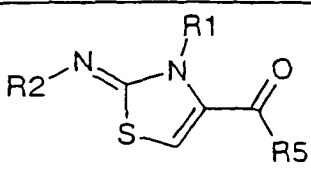
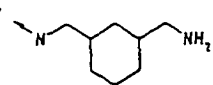
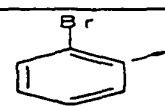
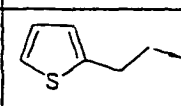
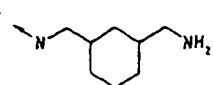
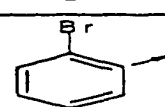
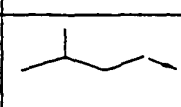
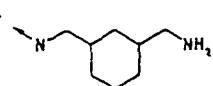
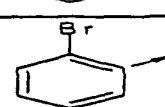
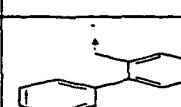
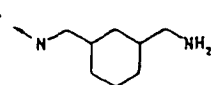
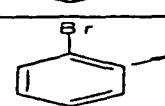
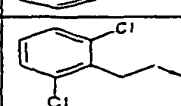
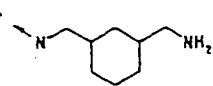
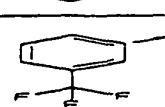
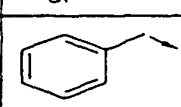
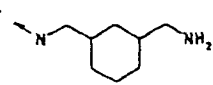
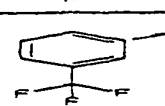
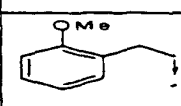
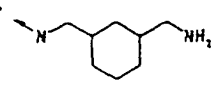
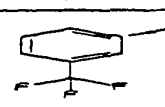
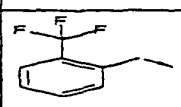
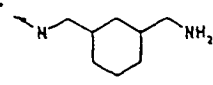
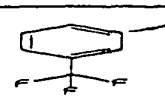
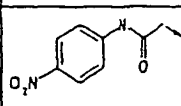
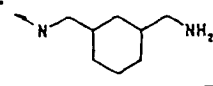
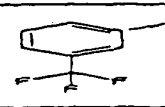
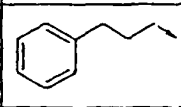
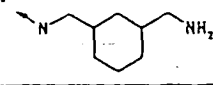
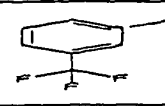
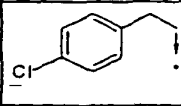
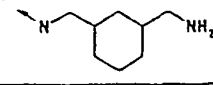
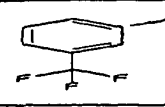
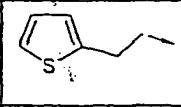
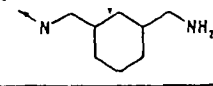
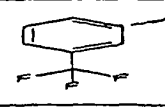
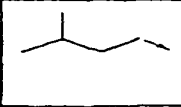
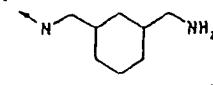
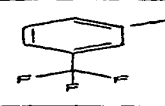
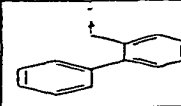
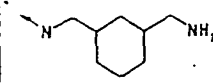
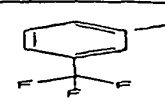
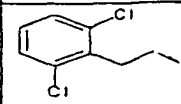
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2240				75.6	5.09	533.17
2241				74.6	5.08	493.26
2242				74.2	5.6	589.22
2243				70	5.48	595.14
2244				63.2	5.24	503.32
2245				61.1	5.1	547.30
2246				63.3	5.65	571.25
2247				63.7	5.15	591.28
2248				67.2	5.46	531.31
2249				76	5.58	551.24
2250				60.2	5.25	523.26
2251				58.8	5.24	483.3
2252				72.1	5.76	579.31
2253				65.2	5.66	585.20

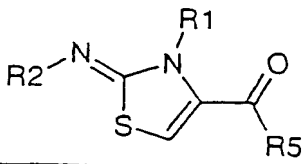
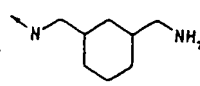

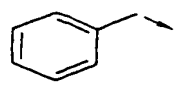
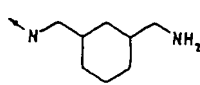
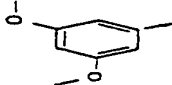
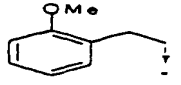
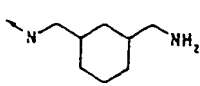
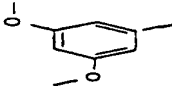
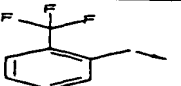
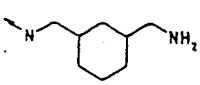

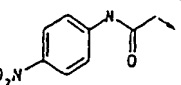
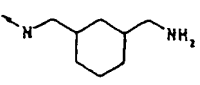

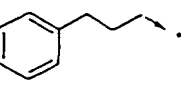
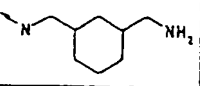
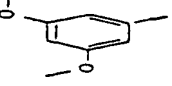
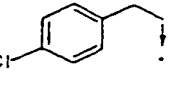
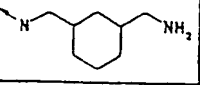

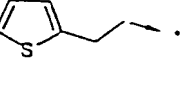
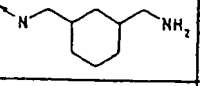
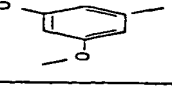
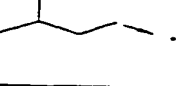
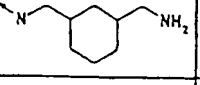
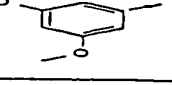
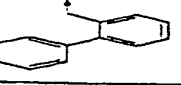
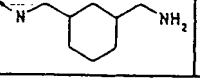
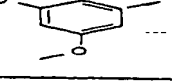
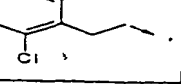
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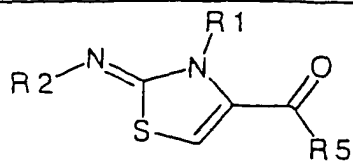
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2254				36	4.36	495.33
2255				58.6	3.97	539.36
2256				70	5.0	563.28
2257				50.2	4.55	583.28
2258				43.2	4.34	523.35
2259				52	4.53	543.29
2260				52.1	4.16	515.30
2261				46.2	4.07	475.38
2262				55.2	4.82	571.33
2263				51.5	4.63	577.22





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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2264				81.1	4.49	465.35
2265				84.1	4.7	481.36
2266				65.7	4.78	445.36
2267				63.0	4.51	399.29
2268				77.8	5.39	555.37
2269				78.5	5.21	485.32
2270				74.0	5.02	557.37
2271				78.1	4.38	525.37
2272				89.2	5.42	527.38
2273				83.0	5.75	537.30
2274				67.8	5.87	525.21
2275				83.2	5.75	541.16
2276				71.9	6.11	505.25
2277				70.5	5.14	459.15

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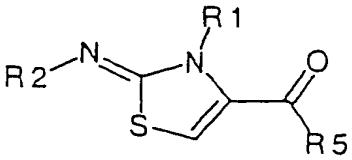
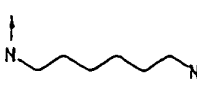
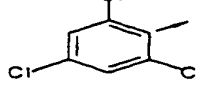
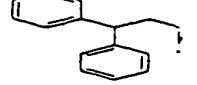
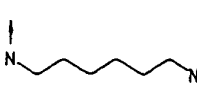
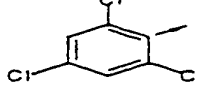
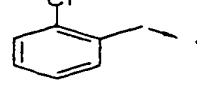
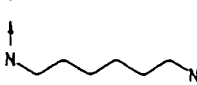
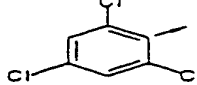
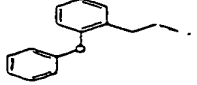
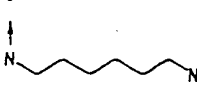
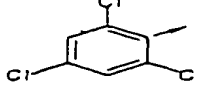
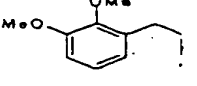
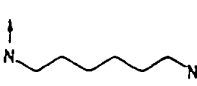
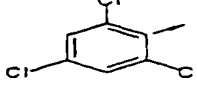
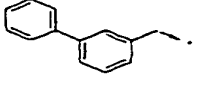
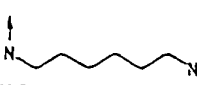
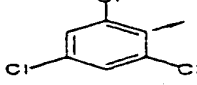
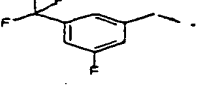
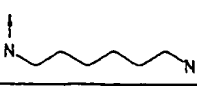
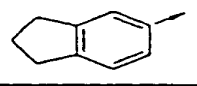
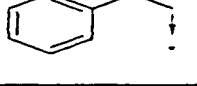
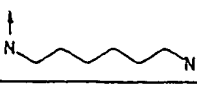
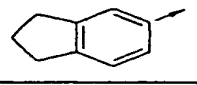
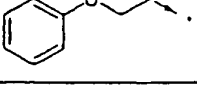

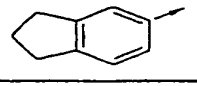
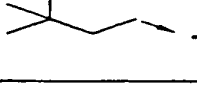
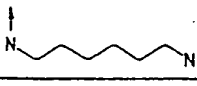
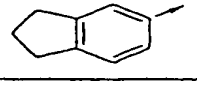
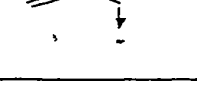
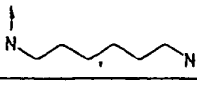
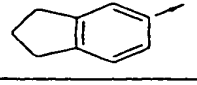
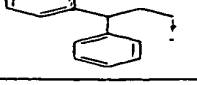
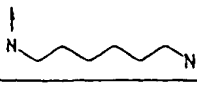
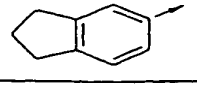
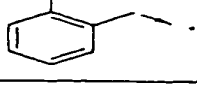
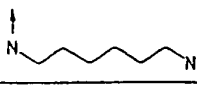
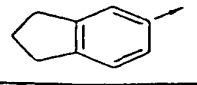
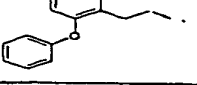
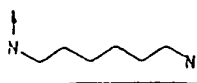
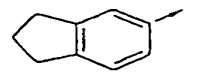
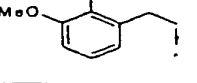
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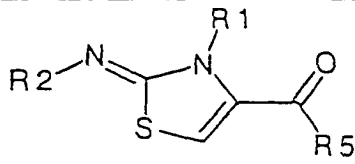
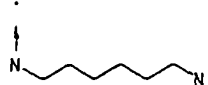
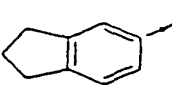
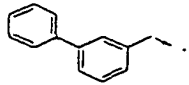
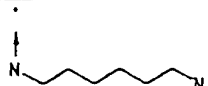
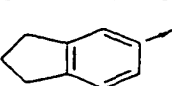
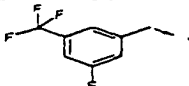
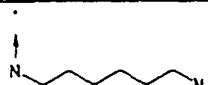
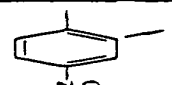
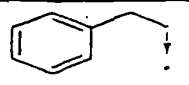

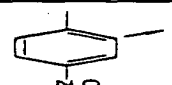
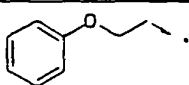

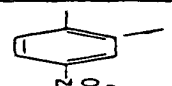
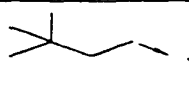
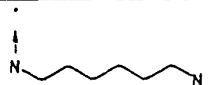
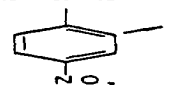
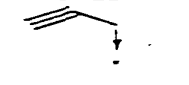
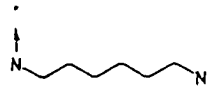
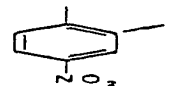
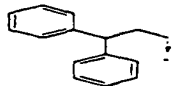
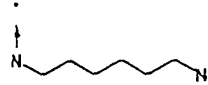
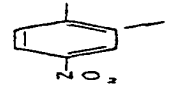
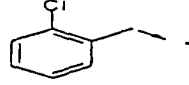
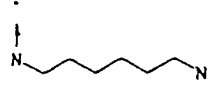
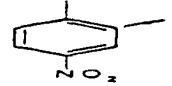
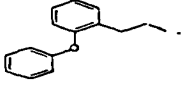
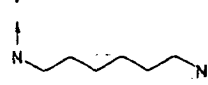
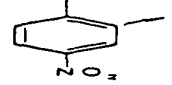
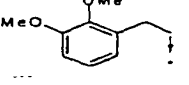
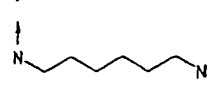
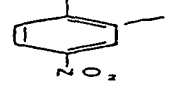
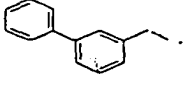
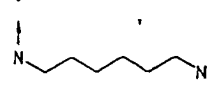
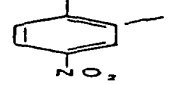
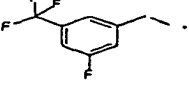
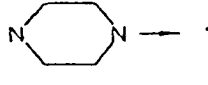
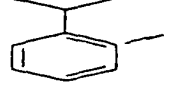
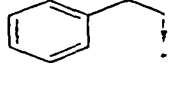
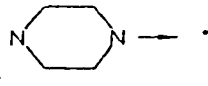
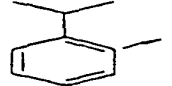
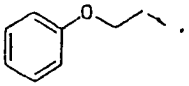
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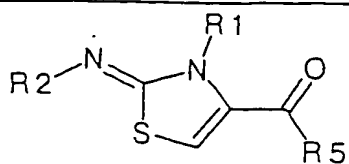
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2278				74.6	6.44	615.23
2279				71.5	5.88	545.10
2280				80.2	6.43	617.19
2281				93.4	5.82	585.18
2282				74.9	6.28	587.19
2283				68.3	6.24	597.14
2284				65.8	4.02	463.35
2285				75.8	4.22	479.33
2286				69.0	4.21	443.37
2287				4.2	4.36	397.33
2288				82.7	4.74	553.37
2289				89.8	4.62	483.29
2290				77.2	4.52	555.33
2291				69.3	3.98	523.35

						
Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2292				73.3	4.98	525.34
2293				73.1	5.44	535.29
2294				59.4	5.14	482.30
2295				76.0	5.09	498.28
2296				62.3	5.47	462.32
2297				58.6	4.55	416.22
2298				79.5	5.84	572.32
2299				74.9	5.3	502.25
2300				72.7	5.71	574.28
2301				71.1	5.06	542.32
2302				73.0	5.66	544.29
2303				64.6	5.62	554.24
2304				92.2	4.62	435.30
2305				90.1	4.67	451.29



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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2306				84.3	4.76	415.32
2307				43.7	4.34	369.27
2308				83.7	5.44	525.34
2309				80.3	4.96	455.25
2310				83.7	5.26	527.32
2311				82.8	4.64	495.34
2312				94.1	5.44	497.32
2313				90.1	5.55	507.29
2314				64.7	5.62	495.16
2315				50.7	5.54	511.15
2316				78.0	5.8	475.22
2317				20.9	4.86	429.14
2318				79.2	6.27	585.15
2319				46.3	5.58	515.12

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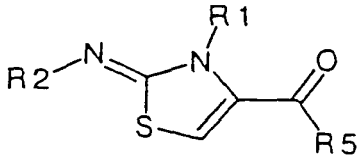

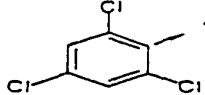
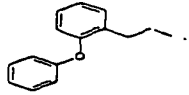

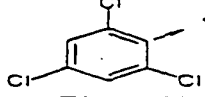
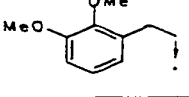
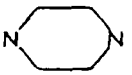
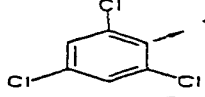
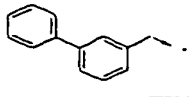

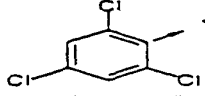
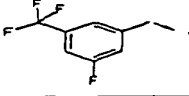

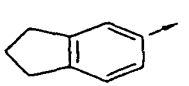
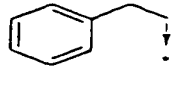
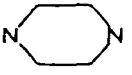
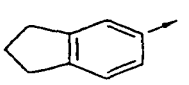
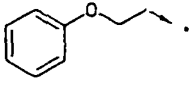
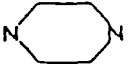
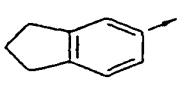
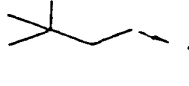
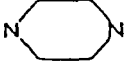
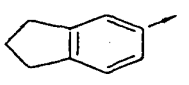
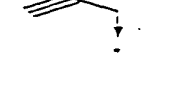

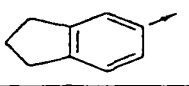
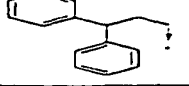

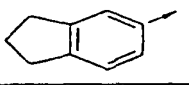
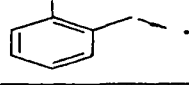

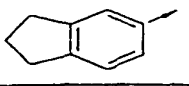
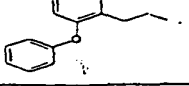

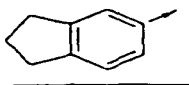
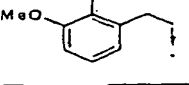

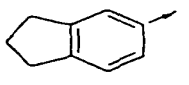
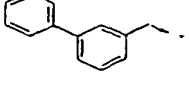

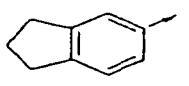
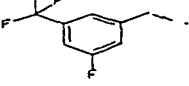
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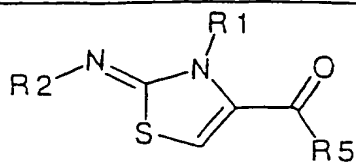
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2320				84.1	6.23	587.20
2321				91.1	5.64	555.18
2322				67.8	6.07	557.22
2323				23.9	5.96	567.17
2324				68.1	4.02	433.40
2325				65.6	4.2	449.38
2326				83.5	4.14	413.39
2327				36.4	3.94	367.35
2328				87.5	4.82	523.39
2329				65.1	4.42	453.33
2330				91.7	4.59	525.37
2331				81.5	4.01	493.40
2332				73.9	4.96	495.39
2333				72.7	5.3	505.33



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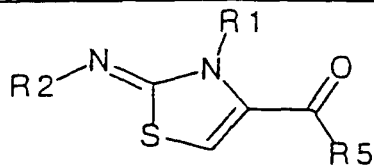
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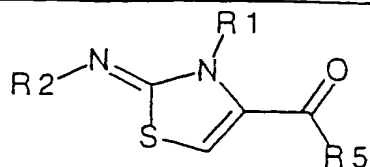
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2334				79.9	4.93	452.35
2335				81.8	4.88	468.33
2336				85.9	5.17	432.36
2337				36.2	4.25	386.28
2338				93.3	5.62	542.36
2339				76.5	4.96	472.3
2340				84.9	5.53	544.34
2341				80.6	4.96	512.34
2342				79.6	5.42	514.35
2343				64.9	5.34	524.27

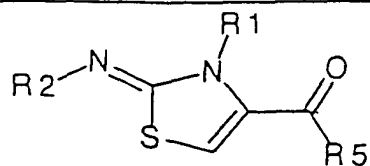


Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2344				76.9	4.54	431.32
2345				80.7	5.47	457.38
2346				82.2	5.19	507.34
2347				82.1	5.38	491.35
2348				76.7	5.2	495.30
2349				83.1	5.42	531.30
2350				78.5	5.4	547.27
2351				86.8	5.58	539.33
2352				79.3	5.37	469.38
2353				83.1	5.18	499.31
2354				82.3	4.32	422.33
2355				78.2	5.26	448.39
2356				79.7	4.98	498.37
2357				80.0	5.2	482.38

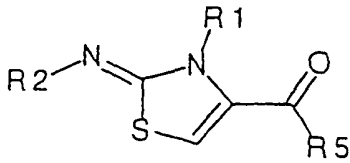

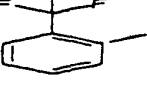
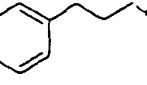

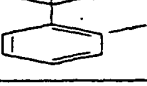
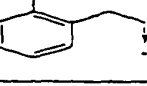

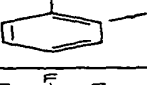
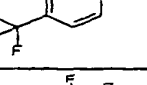
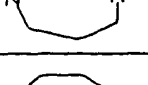
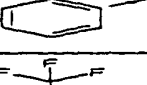
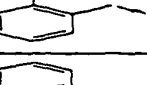
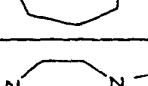
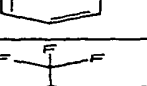
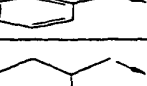
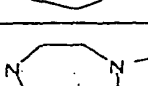
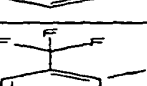
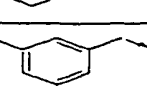
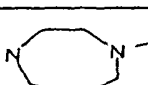
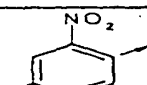
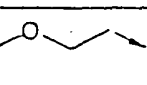

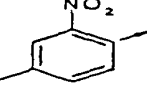
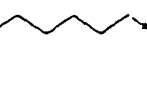

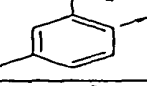
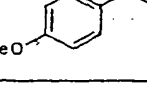

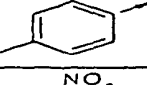
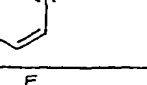
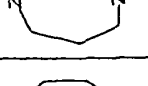
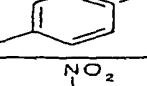

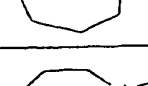
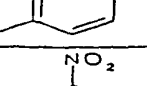
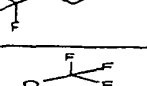
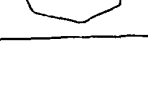
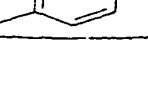
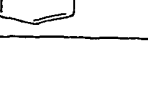





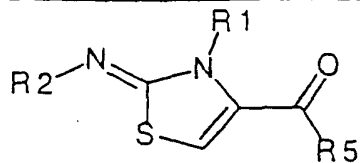
Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2358				75.3	5.0	486.34
2359				81.9	5.26	522.30
2360				77.7	5.25	538.29
2361				83.9	5.4	530.35
2362				81.8	5.16	460.38
2363				79.3	5.03	490.31
2364				82.5	4.01	441.22
2365				80.6	4.98	467.28
2366				82.7	4.72	517.25
2367				83.6	5.0	501.26
2368				84.3	4.9	505.23
2369				82.5	5.48	541.19
2370				86.6	5.5	557.19
2371				85.4	5.53	549.24





Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2372				82.3	4.9	479.30
2373				81.5	5.26	509.21
2374				83.4	4.23	469.37
2375				82.3	4.94	495.40
2376				88.1	4.73	545.36
2377				90.4	4.99	529.39
2378				90.6	4.92	533.35
2379				85.2	5.62	569.33
2380				84.2	5.6	585.33
2381				85.0	5.54	577.38
2382				80.6	4.87	507.41
2383				85.9	5.42	537.34
2384				74.2	5.32	455.34
2385				92.3	5.1	505.32

						
Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2386				78.4	5.23	489.33
2387				71.3	5.12	493.32
2388				74.4	5.32	529.27
2389				68.8	5.29	545.25
2390				77.7	5.44	537.33
2391				80.7	5.24	467.36
2392				63.3	5.04	497.30
2393				87.4	4.16	420.33
2394				82.7	5.12	446.38
2395				82.4	4.88	496.35
2396				78.0	5.04	480.37
2397				75.9	4.9	484.33
2398				71.5	5.16	520.29
2399				65.4	5.12	536.30



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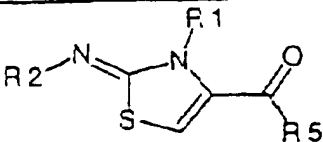
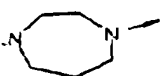
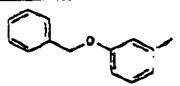

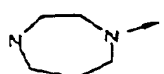
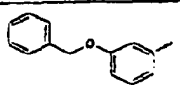
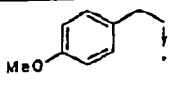
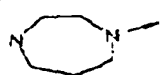
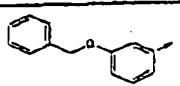

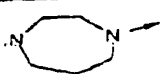
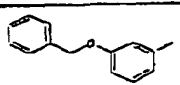
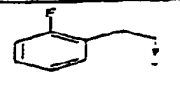
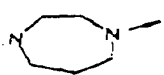
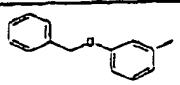
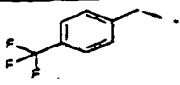

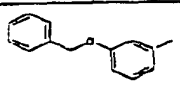
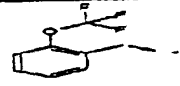
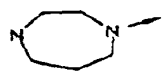
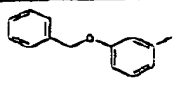
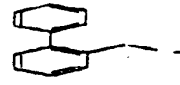
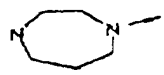
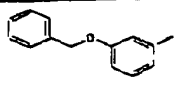
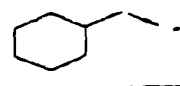

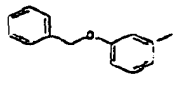
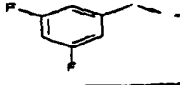
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Ex.	R5	R2	R1	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2400				76.0	5.28	528.33
2401				93.8	5.03	458.38
2402				69.2	4.88	488.30
2403				68.3	3.88	439.23
2404				70.8	4.89	465.28
2405				76.2	4.72	515.23
2406				76.5	4.88	499.27
2407				90.1	4.88	503.26
2408				78.8	5.36	539.19
2409				76.1	5.31	555.17
2410				80.5	5.29	547.22
2411				68.2	4.86	477.30
2412				55.7	5.1	507.20
2413				69.2	4.12	467.36

						
Ex.	R5	R2	R1	Purity (%)	t <sub>r</sub> (min.)	[M+H] <sup>+</sup>
2414				73.6	4.85	493.41
2415				73.9	4.72	543.36
2416				73.4	4.87	527.39
2417				90.6	4.92	531.36
2418				71.6	5.5	567.32
2419				60.5	5.4	583.32
2420				60.8	5.29	575.36
2421				58.8	4.82	505.39
2422				54.7	5.29	535.31

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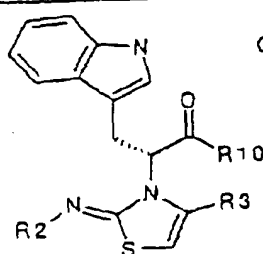

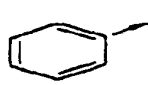
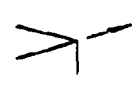
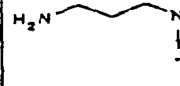


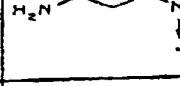
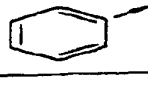
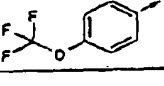


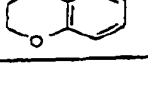
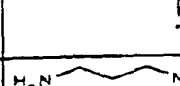
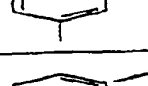

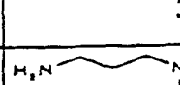
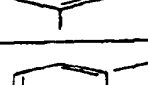
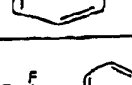
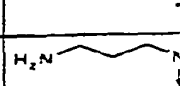
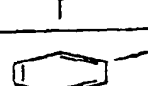
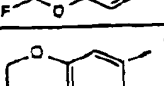
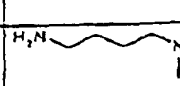
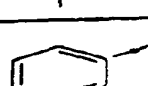
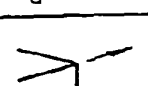
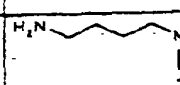


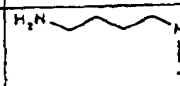
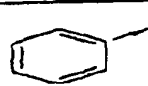
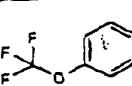
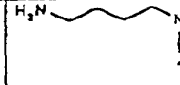
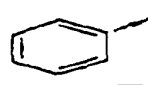
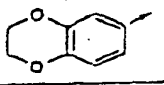






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<div style="display: flex; align-items: center; justify-content: space-between;"> <div style="text-align: center;">  <p>Chiral</p> </div> </div>						
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2423				79.8	3.66	476.30
2424				59.3	3.68	496.26
2425				60.5	4.2	580.22
2426				52.7	3.68	554.24
2427				72.3	3.87	490.30
2428				63.8	3.85	510.26
2429				63.0	4.34	594.23
2430				54.1	3.82	568.25
2431				76.9	3.72	490.30
2432				70.7	3.73	510.26
2433				69.1	4.23	594.24
2434				52.7	3.72	568.24
2435				76.6	3.92	504.32

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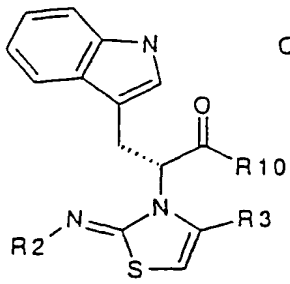
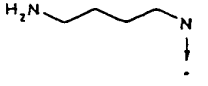

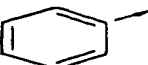


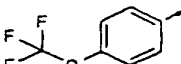


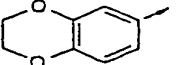
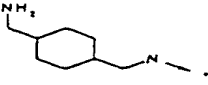
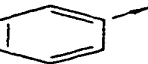
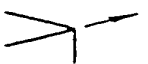
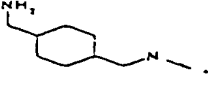

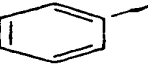
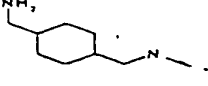
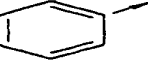
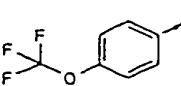
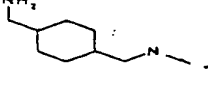
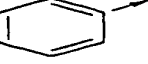
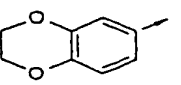
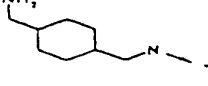

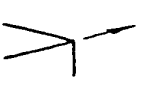
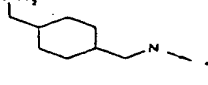


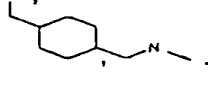

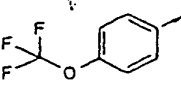
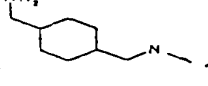

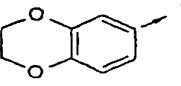
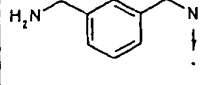
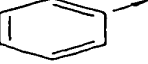
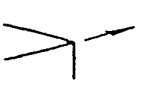
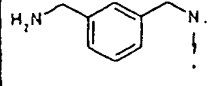

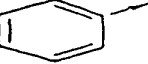
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<div style="display: flex; align-items: center; justify-content: space-between;"> <div style="text-align: center;">  <p>Chiral</p> </div> </div>						
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2436				64.8	3.9	524.28
2437				66.2	4.37	608.24
2438				59.3	3.86	582.27
2439				74.3	3.9	544.32
2440				65.4	3.91	564.29
2441				63.8	4.41	648.30
2442				57.6	3.92	622.31
2443				77.8	4.09	558.34
2444				65.5	4.08	578.30
2445				64.3	4.5	662.31
2446				47.6	4.04	636.36
2447				78.6	3.88	538.28
2448				61.2	3.9	558.24

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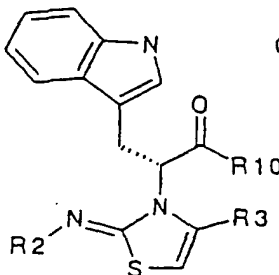
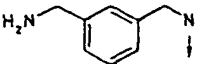
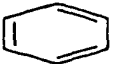
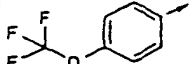
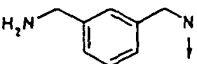
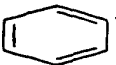
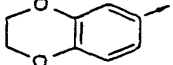
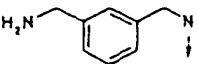

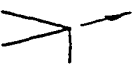
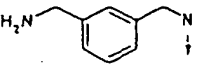
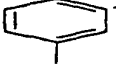
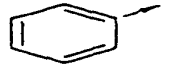
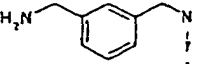
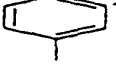
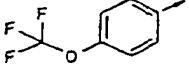
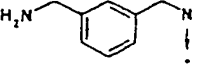
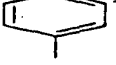
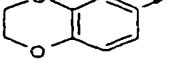
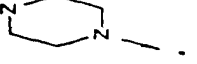
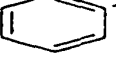
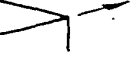
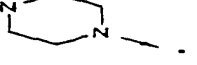


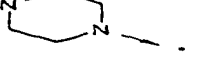

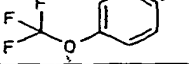
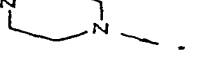
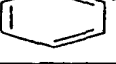
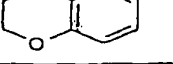
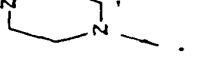
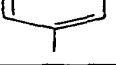
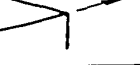
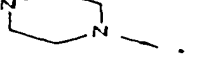
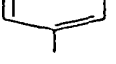

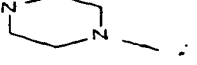
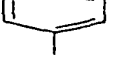
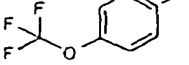
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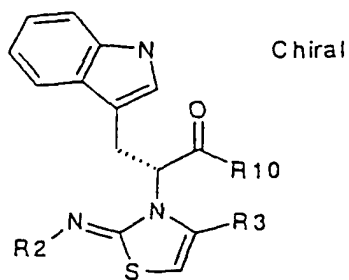
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2449				59.8	4.38	642.27
2450				48.4	3.88	616.30
2451				79.9	4.06	552.28
2452				59.4	4.04	572.25
2453				61.4	4.52	656.29
2454				50.0	4.02	630.31
2455				76.1	3.74	488.29
2456				88.3	3.72	508.25
2457				84.2	4.21	592.22
2458				82.1	3.71	566.24
2459				72.4	3.96	502.32
2460				88.5	3.89	522.27
2461				86.6	4.37	606.26

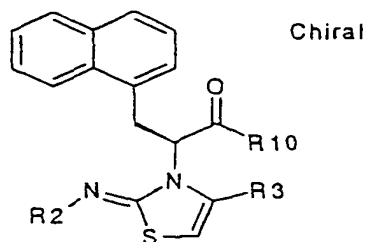
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2462				77.2	3.8	580.26

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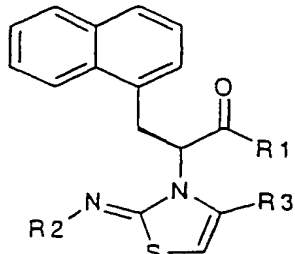

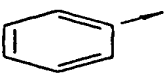

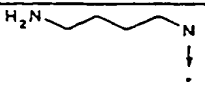
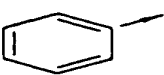
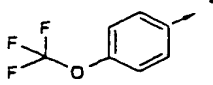
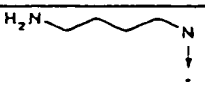

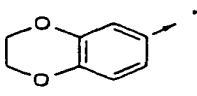
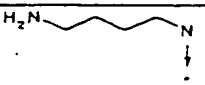

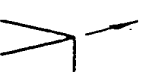
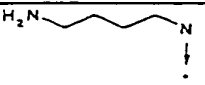


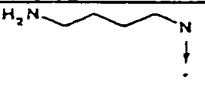

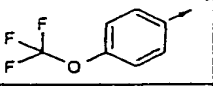
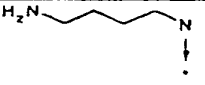
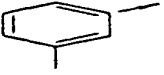
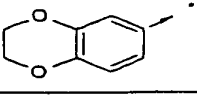
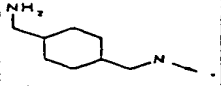
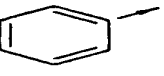
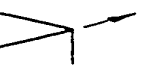
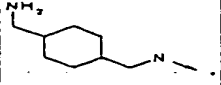
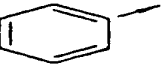
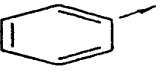
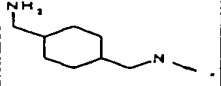
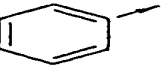
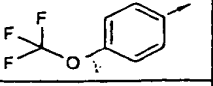
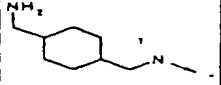
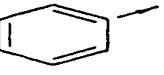
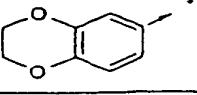
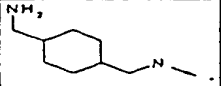

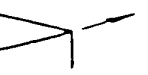
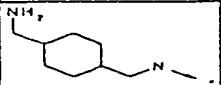

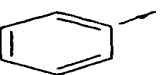
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2463				86.6	3.96	487.31
2464				58.7	4	507.27
2465				64.9	4.48	591.22
2466				40.3	4	565.25
2467				91.3	4.12	501.31
2468				61.2	4.14	521.25
2469				62.4	4.62	605.25
2470				33.1	4.13	579.27
2471				87.3	4.01	501.31

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<div style="display: flex; align-items: center; justify-content: space-between;"> <div style="text-align: center;">  <p>Chiral</p> </div> </div>						
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2472				54.0	4.05	521.25
2473				69.1	4.51	605.26
2474				35.4	4.04	579.27
2475				88.4	4.18	515.31
2476				68.0	4.19	535.28
2477				72.9	4.64	619.25
2478				32.6	4.17	593.28
2479				92.7	4.18	555.33
2480				59.4	4.24	575.29
2481				71.8	4.72	659.33
2482				36.4	4.2	633.44
2483				92.4	4.36	569.34
2484				62.9	4.38	589.32

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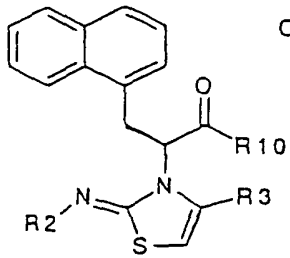
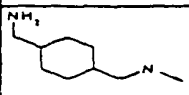

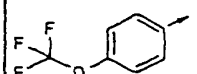
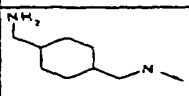

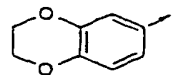
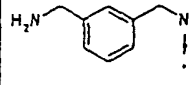
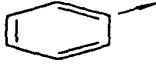
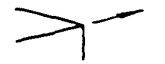
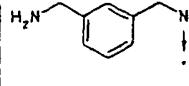
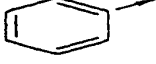
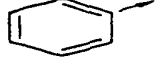
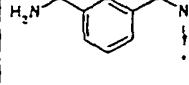

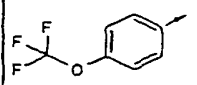
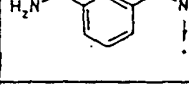

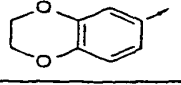

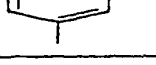

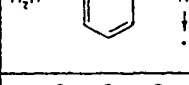
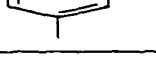
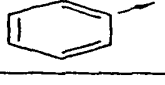
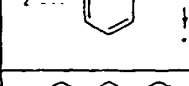
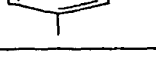
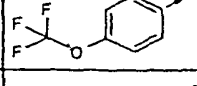
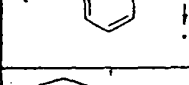
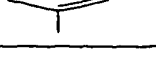
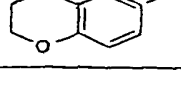
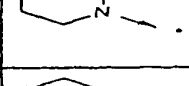
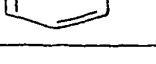

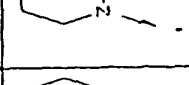

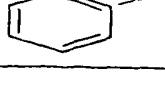
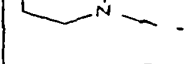
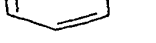
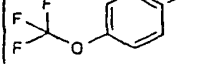
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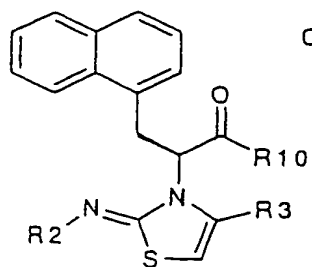
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2485				71.9	4.82	673.33
2486				32.2	4.36	647.19
2487				90.2	4.14	549.28
2488				59.7	4.22	569.24
2489				66.6	4.7	653.25
2490				34.5	4.22	627.27
2491				91.3	4.32	563.30
2492				60.8	4.35	583.26
2493				73.3	4.8	667.27
2494				32.9	4.34	641.29
2495				60.4	3.94	499.30
2496				87.0	3.92	519.24
2497				84.4	4.41	603.24



Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2498				81.4	3.94	577.26
2499				73.9	4.12	513.31
2500				91.5	4.09	533.26
2501				89.6	4.54	617.26
2502				85.4	4.09	591.27

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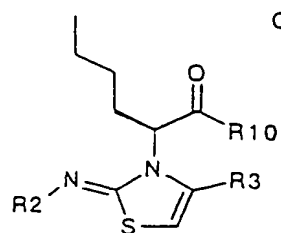
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Chiral						
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2503				77.7	3.8	471.39
2504				37.7	3.82	491.34
2505				79.7	4.09	525.28
2506				58.5	4.23	541.33
2507				84.6	4.0	485.38
2508				73.2	4.0	505.34
2509				82.3	4.25	539.29
2510				74.2	4.37	555.34
2511				57.5	3.56	417.32
2512				66.9	3.56	437.27
2513				69.0	3.85	471.26
2514				71.1	4.0	487.33
2515				76.4	3.76	431.34

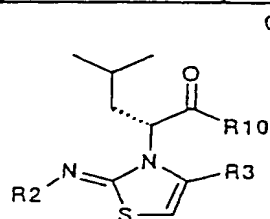
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2516				67.8	3.75	451.30
2517				75.2	4.02	485.27
2518				70.4	4.16	501.32

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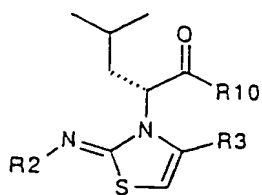
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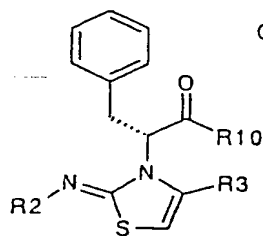
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2519				76.4	3.73	471.38
2520				67.9	3.76	491.33
2521				75.0	4.04	525.28
2522				71.2	4.17	541.34
2523				87.9	3.94	485.39
2524				72.2	3.94	505.34
2525				82.1	4.2	539.30
2526				80.9	4.33	555.34

Chiral



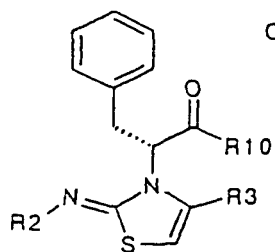
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2527				70.7	3.51	417.32
2528				50.3	3.52	437.28
2529				72.4	3.8	471.26
2530				74.5	3.96	487.32
2531				84.4	3.72	431.32
2532				68	3.71	451.29
2533				89.6	3.98	485.26
2534				77.9	4.12	501.32

Chiral



Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2535				84.7	3.83	505.34
2536				75.2	3.89	525.30

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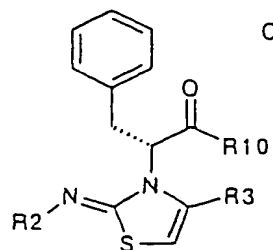
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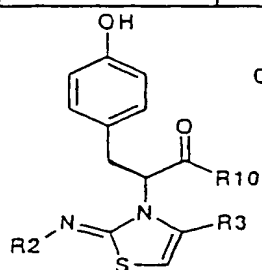
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2537				75.9	4.17	559.25
2538				70.4	4.29	575.30
2539				90.9	4.03	519.35
2540				71.5	4.04	539.31
2541				79.2	4.31	573.25
2542				80.6	4.43	589.33
2543				77.2	3.62	451.30
2544				69.9	3.65	471.27
2545				74.8	3.92	505.22
2546				66.7	4.06	521.26
2547				83.5	3.82	465.31
2548				72.9	3.82	485.28
2549				33.1	4.1	519.23

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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2550				51.2	4.22	535.28

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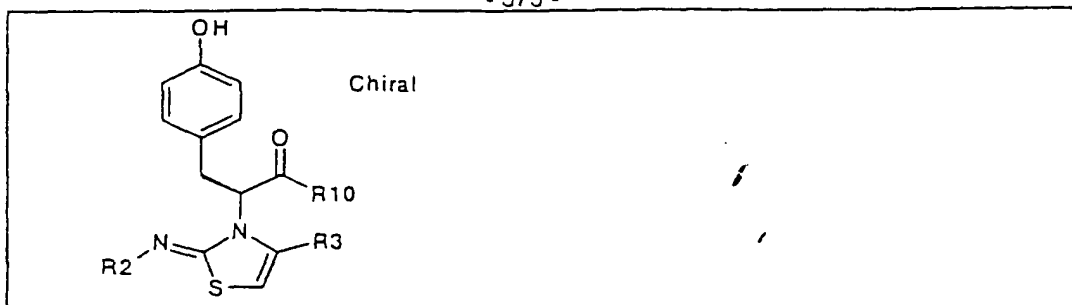
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2551				79.8	3.45	521.33
2552				72.6	4.14	541.29
2553				63.7	3.79	575.24
2554				73.8	3.93	591.31
2555				91.2	3.65	535.35
2556				75.6	3.66	555.29
2557				78.3	3.94	589.26
2558				69.7	4.06	605.35
2559				69.1	3.22	467.29

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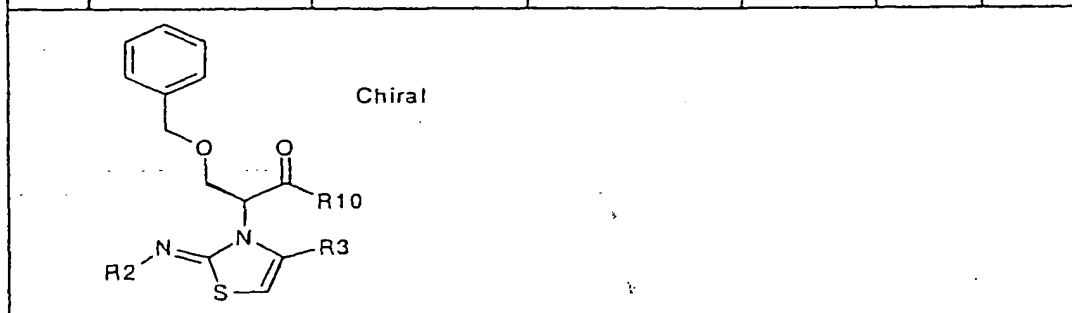
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2560				73.7	3.26	487.27
2561				79.6	3.56	521.20
2562				73.5	3.72	537.27
2563				86.1	3.42	481.31
2564				77.1	3.43	501.29
2565				83.0	3.73	535.22
2566				71.9	3.86	551.28

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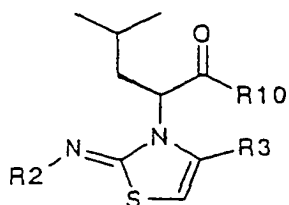
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2567				82.0	3.99	535.3
2568				40.6	4.04	555.31
2569				47.5	4.31	589.26

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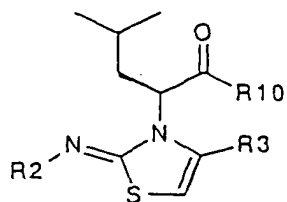


Chiral



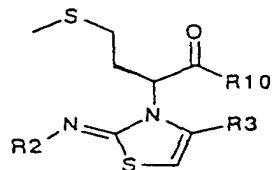
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2583				52.2	3.91	465.24
2584				55.9	4	529.14
2585				51.3	3.9	445.29
2586				57.4	3.9	510.24
2587				54.3	4.04	479.28
2588				61.7	4.12	543.15
2589				80.0	3.82	465.25
2590				61.6	3.85	530.20
2591				61.1	3.97	499.25
2592				61.3	4.06	563.1
2593				84.2	3.96	479.29
2594				58.8	3.98	544.20

Chiral



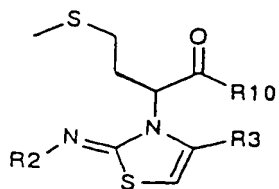
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2595				61.5	4.1	513.26
2596				65.5	4.19	577.1

Chiral



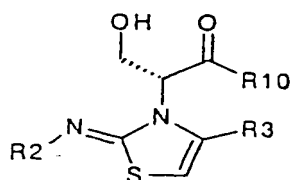
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2597				28.6	3.7	514.16
2598				39.0	3.83	483.24
2599				39.9	3.92	547.1
2600				53.5	3.8	463.26
2601				28.8	3.83	528.19
2602				31.0	3.96	497.24
2603				34.0	4.05	561.1
2604				64.5	3.72	483.24

Chiral



Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2605				25.4	3.78	548.12
2606				36.8	3.9	517.20
2607				31.2	4	581.1
2608				72.8	3.86	497.24
2609				31.7	3.9	562.17
2610				40.1	4.02	531.21
2611				38.2	4.12	595.1

Chiral



Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2612				45.2	3.49	419.24
2613				56.6	3.39	439.21
2614				58.6	3.56	453.23

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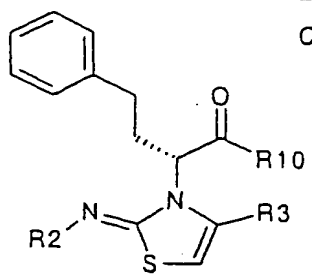
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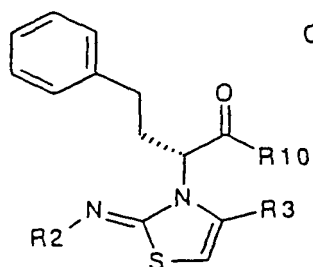
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2615				65.5	3.96	479.28
2616				50.5	4	544.19
2617				55.7	4.11	513.26
2618				55.5	4.2	577.13
2619				67.1	4.09	493.30
2620				53.7	4.11	558.20
2621				55.5	4.22	527.27
2622				72.1	4.3	591.13
2623				81.1	4.02	513.26
2624				51.0	4.08	578.18
2625				54.1	4.17	547.21
2626				65.2	4.26	611.11
2627				83.9	4.16	527.27

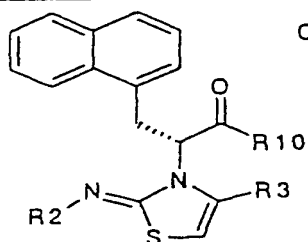
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2628				60.2	4.18	592.21
2629				63	4.3	561.21
2630				74.0	4.36	625.11

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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2631				83.1	4.06	515.26
2632				57.8	4.13	580.20
2633				37.4	4.22	549.23
2634				43.3	4.31	613.12
2635				86.7	4.18	529.27
2636				64.3	4.22	594.19
2637				37.0	4.32	563.25

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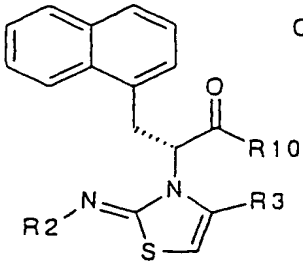
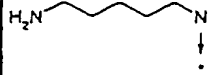

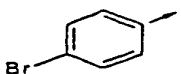
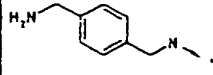
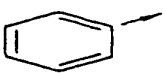
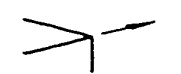
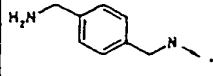
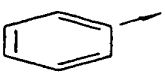
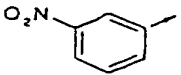
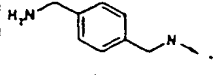
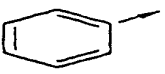
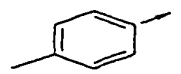
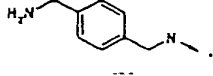
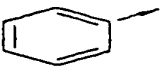
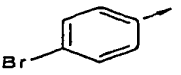
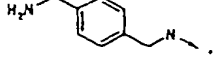

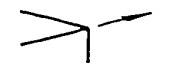
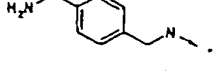
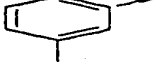
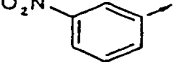
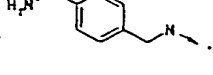

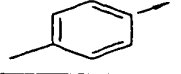
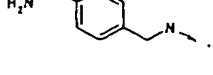

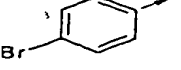
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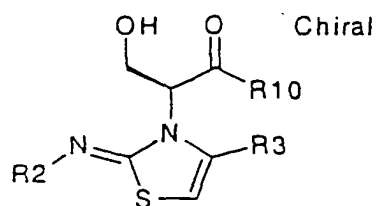
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2638				44.3	4.4	627.15
2639				86.9	4.14	549.23
2640				53.4	4.23	614.17
2641				37	4.3	583.21
2642				45.7	4.4	647.11
2643				88.9	4.24	563.25
2644				57.3	4.3	628.19
2645				39.4	4.39	597.22
2646				44.1	4.48	661.15





Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2647				25.6	3.18	495.23
2648				33.1	3.59	533.15
2649				27.0	3	490.2
2650				33.6	3.14	562.16
2651				27.2	3.36	509.21
2652				32.5	3.76	547.16
2653				29.7	3.2	504.2
2654				34.8	3.32	576.21
2655				73.7	2.93	439.15
2656				60.6	3.37	477.14
2657				65.1	2.7	434.1
2658				69.3	2.92	506.14
2659				72.5	3.14	453.17
2660				77.2	3.55	491.14

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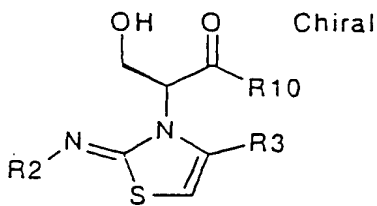
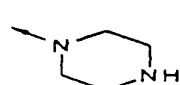
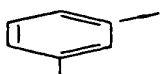
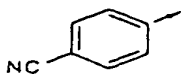
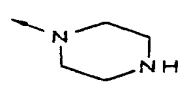

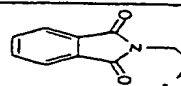
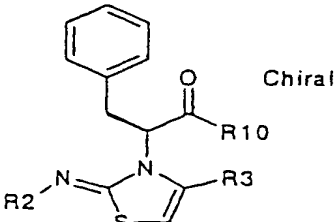
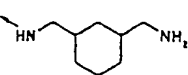
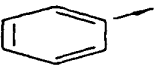
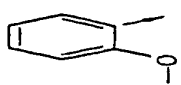
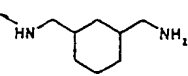
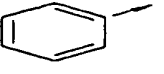
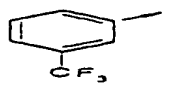
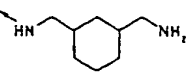
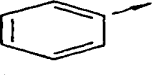
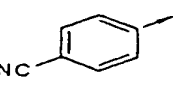
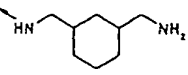
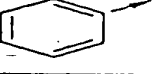
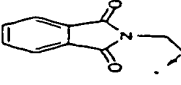
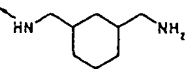

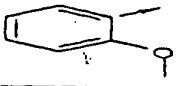
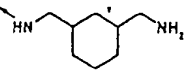
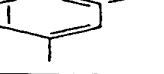
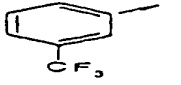
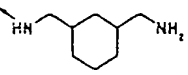

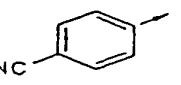
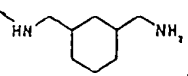
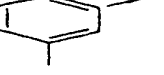
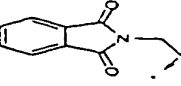
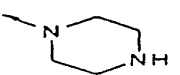
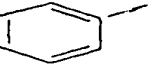
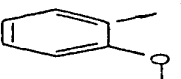
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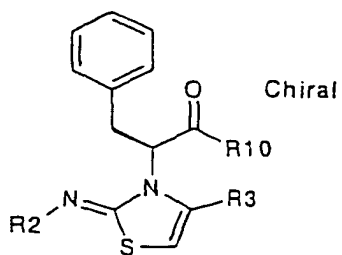
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<div>  <p>Chiral</p> </div>						
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2661				66.4	2.9	448.1
2662				65.9	3.14	520.15
<div>  <p>Chiral</p> </div>						
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2663				63.3	3.82	555.21
2664				85.8	4.24	593.19
2665				87.5	3.8	550.2
2666				75.1	3.78	622.22
2667				66.1	3.98	569.21
2668				87.2	4.35	607.21
2669				82.9	3.9	564.2
2670				79.1	3.94	636.25
2671				82.0	3.55	499.18

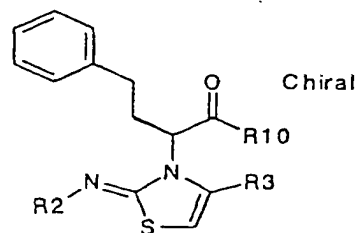
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2672				82.2	3.93	537.14
2673				86.4	3.4	494.2
2674				90.4	3.52	566.15
2675				88.0	3.72	513.19
2676				88.8	4.08	551.15
2677				88.9	3.6	508.2
2678				93.6	3.7	580.17

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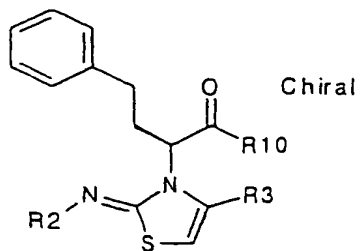


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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2679				59.5	4	569.20
2680				82.6	4.37	607.21
2681				74.9	3.9	564.2

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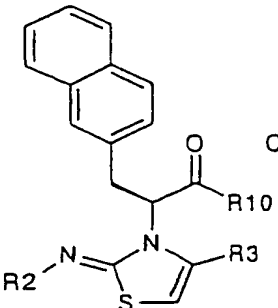
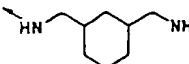
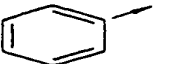
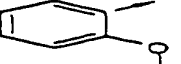
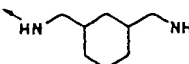
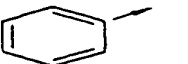
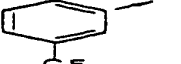
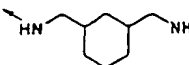
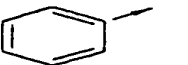
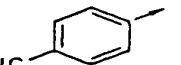
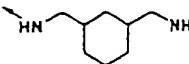
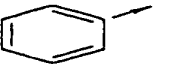
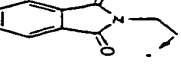
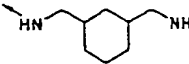
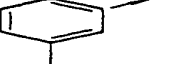
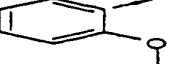
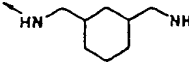
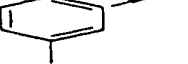
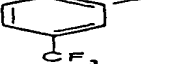
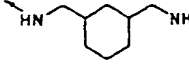
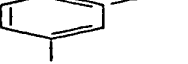
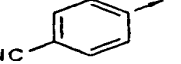
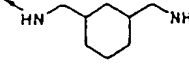
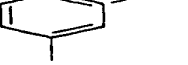
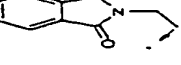
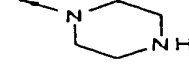
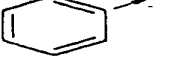
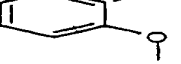
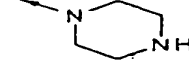
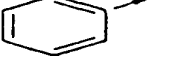
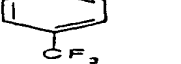
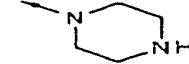
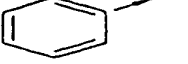
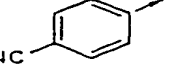
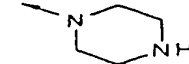
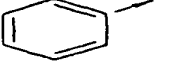
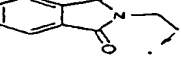
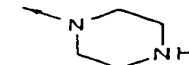
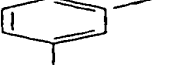
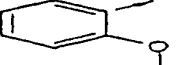
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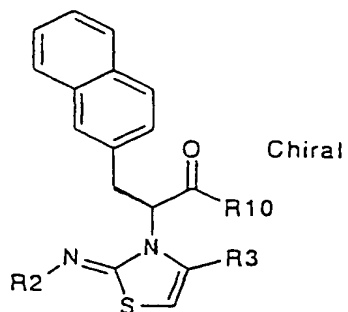
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2682				70.6	3.94	636.26
2683				55.3	4.14	583.24
2684				85.3	4.49	621.22
2685				86.1	4.1	578.2
2686				72.7	4.09	650.26
2687				87.5	3.74	513.20
2688				86.1	4.1	551.16
2689				87.4	3.6	508.2
2690				87.9	3.73	580.18
2691				87.2	3.89	527.21
2692				88.3	4.24	565.15
2693				89.8	3.8	522.2
2694				92.5	3.86	594.17

5	<div style="display: flex; align-items: center; justify-content: center;">  <div style="margin-left: 10px;">Chiral</div> </div>						
	Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
10	2695				69.9	4.14	605.25
	2696				81.8	4.55	643.21
15	2697				65.3	4.1	600.2
	2698				69.2	4.11	672.25
20	2699				74.0	4.28	619.24
	2700				69.3	4.67	657.24
25	2701				75.9	4.3	614.2
	2702				84.8	4.27	686.27
30	2703				86.6	3.91	549.16
	2704				77.7	4.26	587.13
35	2705				69.4	3.8	544.1
	2706				88.0	3.9	616.19
	2707				79.9	4.06	563.18

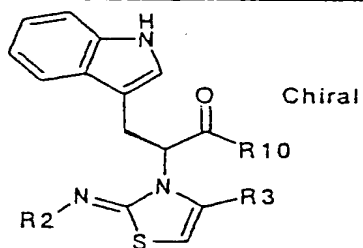
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2708				75.9	4.38	601.14
2709				62	3.9	603.2
2710				87.7	4.05	630.21

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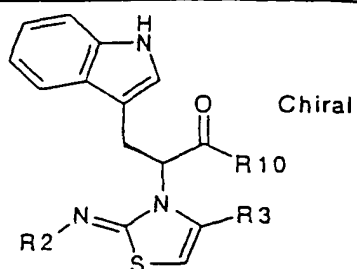
Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2711				56.8	3.85	594.20
2712				69.7	4.18	632.22
2713				62.2	3.7	589.2
2714				79.2	3.76	661.23
2715				56.8	4	608.23
2716				70.5	4.31	646.23
2717				62	3.9	603.2

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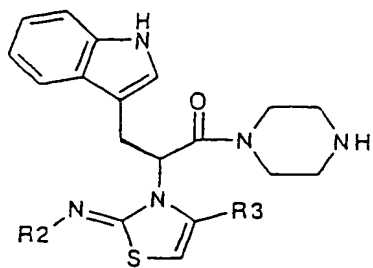
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Ex.	R10	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2718				76.9	3.92	675.26
2719				75.5	3.63	538.18
2720				79.4	3.96	576.13
2721				73	3.5	533.2
2722				87.0	3.56	605.17
2723				81.8	3.8	552.18
2724				80.1	4.11	590.15
2725				79.4	3.6	547.2
2726				86.3	3.73	619.18

Chiral



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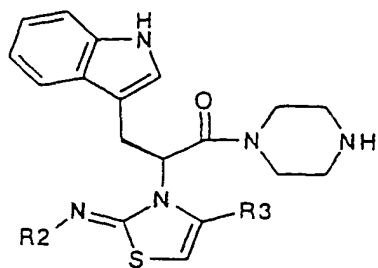
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2727			73.7	4.7	488.3
2728			87.1	4.2	508.2
2729			90.3	4.3	522.3
2730			78.2	4.5	586.1
2731			73	4.1	533.2
2732			86.4	4.5	542.2
2733			77.7	4.6	576.2
2734			80	4.7	592.2
2735			76.4	4.9	644.2
2736			81.4	4.6	558.2
2737			79.8	4.4	502.3



Chiral



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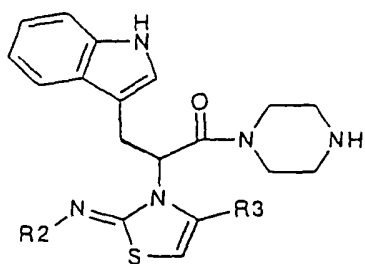
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Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2738			87.5	4.4	522.3
2739			91.4	4.5	536.3
2740			83.3	4.6	600.1
2741			82	4.3	547.2
2742			83.9	4.6	556.2
2743			85.4	4.7	590.2
2744			85.2	4.8	606.2
2745			82	4.3	658.2
2746			86.7	4.7	572.2
2747			31.6	4.3	506.3
2748			71.1	4.3	526.2

Chiral



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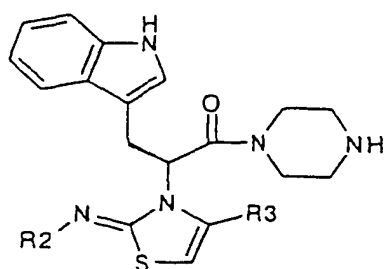
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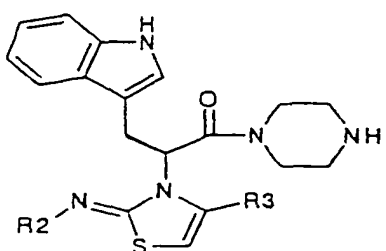
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2749			89.5	4.4	540.2
2750			59.6	4.5	604.1
2751			51.3	4.2	551.2
2752			62.2	4.5	560.2
2753			59.6	4.7	594.2
2754			63	4.7	610.2
2755			52.5	4.9	662.2
2756			67.8	4.6	576.1
2757			81.1	4.6	516.3
2758			85.8	4.5	536.3
2759			85.4	4.7	550.3

Chiral



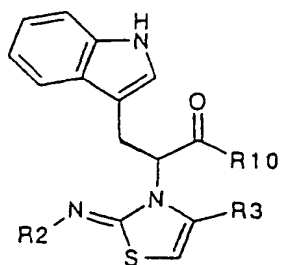
Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2760			76.6	4.7	614.1

Chiral



Ex.	R2	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2761			77.2	4.4	561.2
2762			85.4	4.7	570.2
2763			79.7	4.8	604.2
2764			81.1	4.9	620.2
2765			79.2	5.1	672.2
2766			82	4.8	586.3

Chiral



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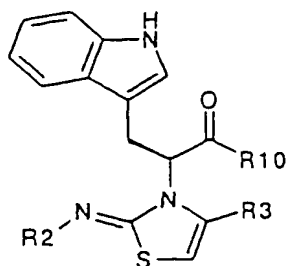
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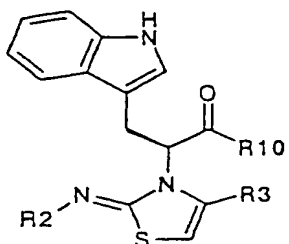
Ex.	R2	R10	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2767				64.3	3.91	530.20
2768				58.3	3.57	521.22
2769				66.7	4.03	564.20
2770				65.1	3.71	541.19
2771				56.1	3.58	521.21
2772				42.1	3.93	544.19
2773				34.6	3.59	535.22
2774				46.9	4.05	578.21
2775				33.3	3.73	555.19
2776				33.4	3.6	535.22
2777				39.6	3.97	558.22

Chiral



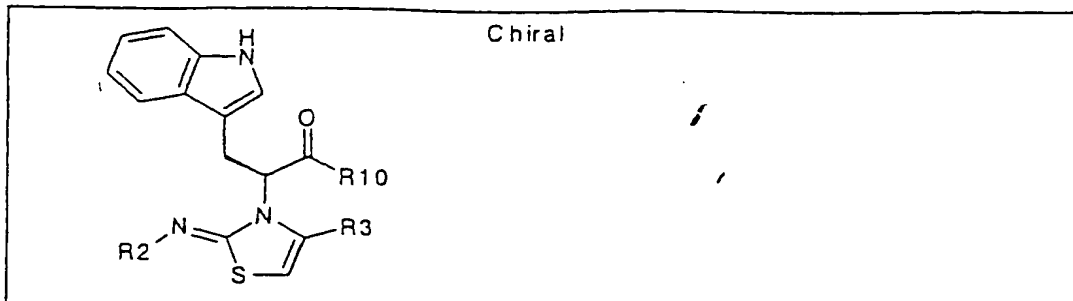
Ex.	R2	R10	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2778				47.5	3.63	549.23
2779				50.3	4.09	592.23

Chiral



Ex.	R2	R10	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2780				40.6	3.76	569.19
2781				42.7	3.63	549.25
2782				35.5	4.0	572.17
2783				33.2	3.69	563.26
2784				45	4.1	606.27
2785				36.0	3.82	583.23

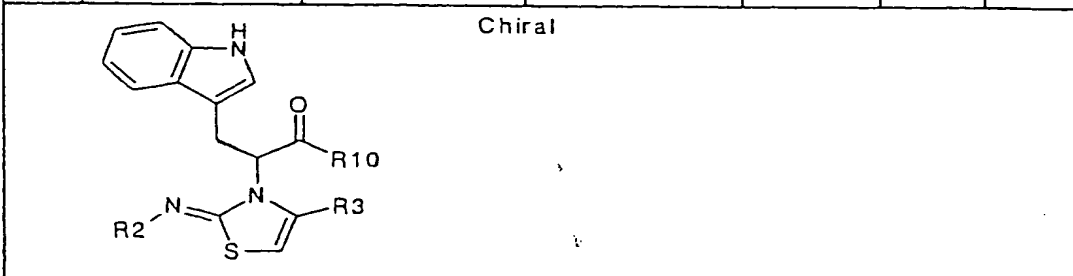
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Ex.	R2	R10	R3	Pureté (%)	tr (min)	[M+H] <sup>+</sup>
2786				27.1	3.7	563.26
2787				73.6	3.98	530.19
2788				62.5	3.64	521.21
2789				74.8	4.09	564.2
2790				67.7	3.77	541.20
2791				71.3	3.65	521.21
2792				52.4	4,0	544.18

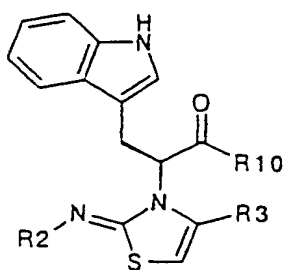
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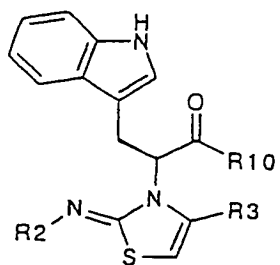
Ex.	R2	R10	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2793				47.0	3.65	535.22

Chiral



Ex.	R2	R10	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2794				54.7	4.11	578.22
2795				43.7	3.79	555.20
2796				44.6	3.67	535.22
2797				53.7	4.03	558.20
2798				51.0	3.69	549.23
2799				56.5	4.15	592.23
2800				48.9	3.83	569.20
2801				46.0	3.7	549.24
2802				41.2	4.1	572.21
2803				36.7	3.76	563.26
2804				47.4	4.2	606.26

Chiral



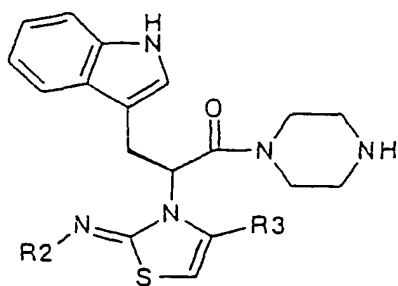
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Ex.	R2	R10	R3	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2805				37.0	3.89	583.22
2806				37.3	3.76	563.26

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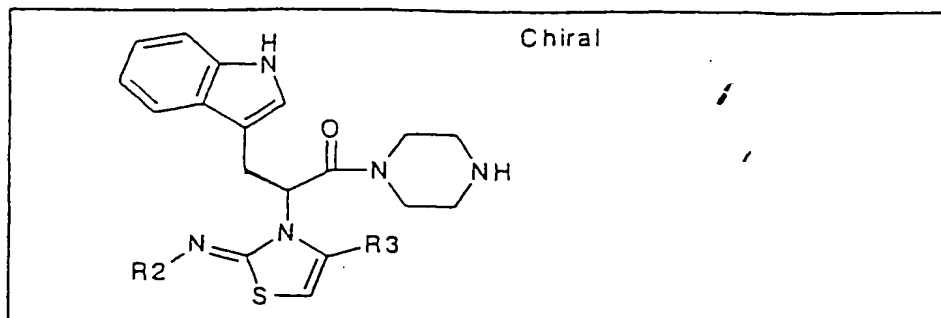


Chiral



Ex.	R3	R2	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2807			52.1	3.65	547.22
2808			61.7	3.61	563.24
2809			54.1	3.91	561.26
2810			56.7	3.69	563.23
2811			54.7	3.65	547.23
2812			63.6	3.96	561.25
2813			66.1	4.13	575.26
2814			34.9	4.29	589.29
2815			69.3	3.66	563.24
2816			47.6	3.66	547.23
2817			41.4	3.61	563.23

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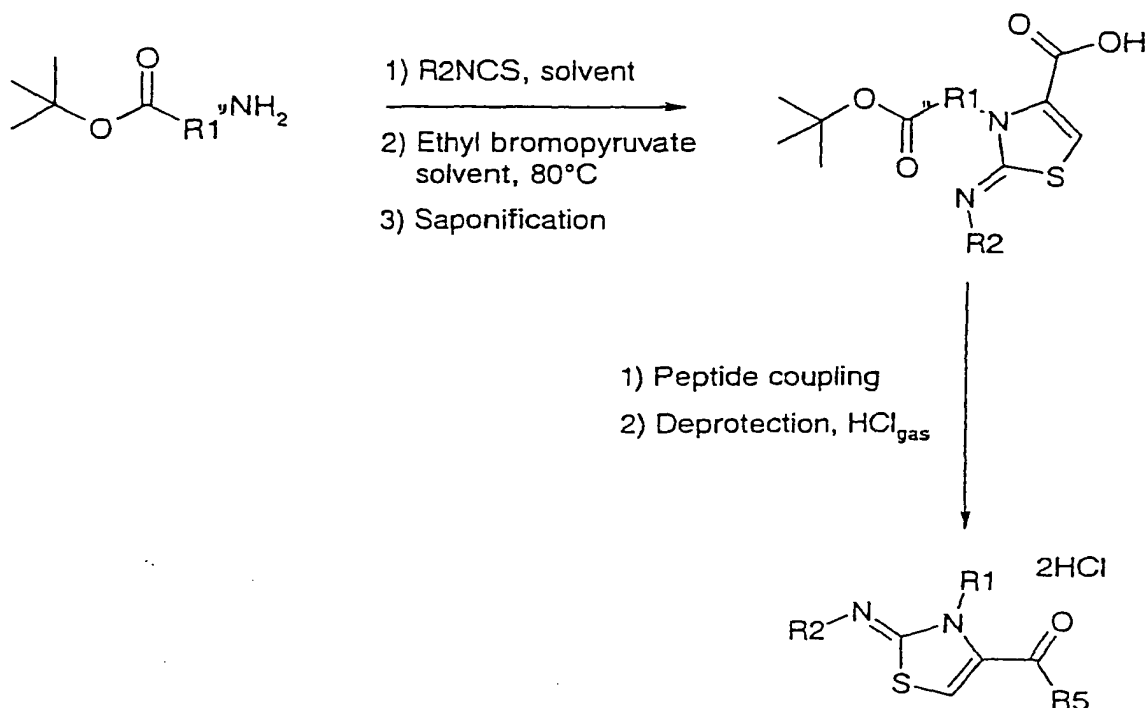
Ex.	R3	R2	Purity (%)	rt (min.)	[M+H] <sup>+</sup>
2818			28.5	3.97	561.24
2819			56.4	3.71	563.23
2820			45.6	3.65	547.22
2821			62.6	3.99	561.24
2822			42.0	4.17	575.26
2823			45.7	4.32	589.28
2824			23.5	3.65	551.21
2825			70.9	3.67	563.22

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Some compounds according to the invention can be obtained according to method G described hereafter.

### METHOD G

Synthesis in solution of 2-iminothiazole-4-carboxamide derivatives from  
5 monoprotected symmetrical diamines (Boc)



#### General procedure:

The monoprotected symmetrical diamine (Boc) (1 equiv) is agitated overnight with an aromatic isothiocyanate (1 equiv) at ambient temperature in an anhydrous solvent such as dioxane, dimethylformamide or chloroform., 1 equivalent of an inorganic base such as sodium or potassium hydrogen carbonate and 1 equivalent of ethyl bromopyruvate dissolved beforehand in an anhydrous solvent such as dioxane or dimethylformamide is successively added to the crude isothioureia intermediate. The mixture is then heated at 80 °C for 1 to 3 hours and the inorganic salts are eliminated by filtration. The solvents are evaporated off under vacuum and the residue is purified by flash chromatography on silica gel using an ethyl acetate / heptane gradient. Saponification of the ester intermediate is carried out in a solvent such as tetrahydrofuran using a 1N solution of KOH, LiOH or NaOH. The mixture is agitated vigorously for 6 to 20 hours at ambient temperature then acidified with a 1N aqueous solution of hydrochloric acid to pH 2.5.

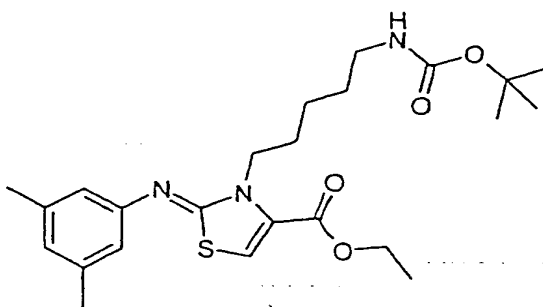
The organic phase is extracted several times with dichloromethane then the organic phase is washed with water until neutral pH and dried over sodium sulphate.

A primary or secondary amine (1.1 to 2 equiv.) pre-dissolved in an anhydrous solvent such as dimethylformamide is added under argon to a solution of carboxylic acid intermediate (1 equiv.) and a peptide coupling agent such as DIC, DIC/HOBt, HATU or TBTU (1.1 to 2 equiv.), dissolved beforehand in an anhydrous solvent such as dimethylformamide. The mixture is agitated overnight at ambient temperature. The solvent is evaporated off under vacuum and the residue purified by flash chromatography on silica gel using an ethyl acetate / heptane gradient. The carboxamide intermediate is diluted in a solvent such as dichloromethane or ethyl acetate and deprotected after passage through the solution of a current of dry hydrogen chloride for 1 to 6 hours at ambient temperature. The corresponding dihydrochloride is isolated either by filtration of the precipitate or, after evaporation under vacuum of the solvent, by adding diethylether for better crystallisation.

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#### Preparation 25

*ethyl (2Z)-3-{5-[(tert-butoxycarbonyl)amino]pentyl}-2-[(3,5-dimethylphenyl)imino]-2,3-dihydro-1,3-thiazole-4-carboxylate*  
(C<sub>24</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub>S; MM = 461.63)



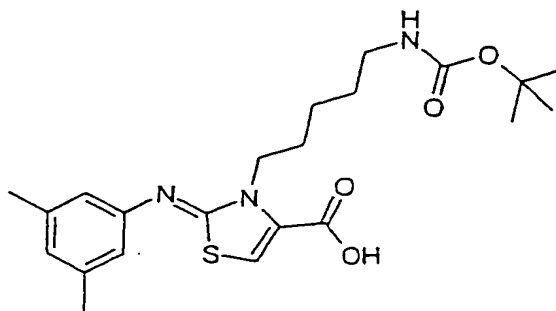
*N*-Boc-1,5-diaminopentane (1.04 g; 5 mmol) is agitated with 3,5-dimethylisothiocyanate (824 mg; 5 mmol) in 10 ml anhydrous dioxane. 420 mg (5 mmol) of sodium hydrogen carbonate and 1.08 g (5 mmol) of ethyl bromopyruvate dissolved beforehand in 2 ml of anhydrous dioxane are successively added to the crude isothioureia intermediate. The mixture is then heated at 80 °C for one hour and the inorganic salts are eliminated by filtration. The dioxane is evaporated off under vacuum and the yellow residue is purified by flash chromatography on silica gel (eluent: ethyl acetate / heptane 2:8 then 3:7). A yellow oil (1.8 g; yield of 77.9%) corresponding to the expected compound is then isolated.

NMR  $^1\text{H}$  (DMSO- $d_6$ , 400 MHz)  $\delta$ : 7.23 (s, 1H); 6.71 (broad s, 1H); 6.65 (s, 1H); 6.54 (s, 2H); 4.26 (q, 2H,  $J = 6.4$  Hz); 4.13 (t, 2H,  $J = 6.4$  Hz); 2.9 (q, 2H,  $J = 6$  Hz); 2.22 (s, 6H); 1.63 (m, 2H); 1.4 (m, 2H); 1.36 (s, 9H); 1.29-1.23 (m, 2H + 3H). MS/LC:  $m/z = 462.3$  (M+H) $^+$ .

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#### Preparation 26

(2Z)-3-{5-[(*tert*-butoxycarbonyl)amino]pentyl}-2-[(3,5-dimethylphenyl)imino]-2,3-dihydro-1,3-thiazole-4-carboxylic acid  
( $\text{C}_{22}\text{H}_{31}\text{N}_3\text{O}_4\text{S}$ ; MM = 433.57)

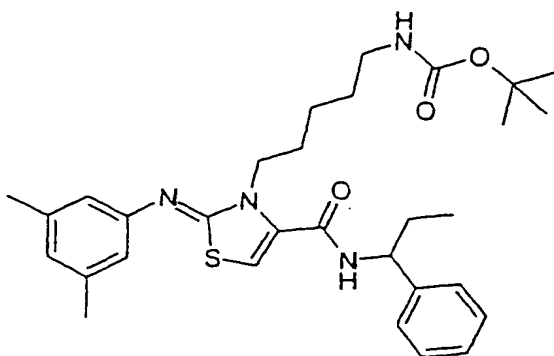


10 The compound of Preparation 25 (1.77 g; 3.83 mmol) is dissolved in 20 ml of tetrahydrofuran and treated with 15 ml of a 1N aqueous solution of NaOH. The mixture is agitated vigorously for 6 hours at ambient temperature. The carboxylate is then acidified with a 1N aqueous solution of hydrochloric acid to pH 2.5. The aqueous phase is extracted with dichloromethane (4 x 50 ml) and the organic phases are washed with water until neutral pH and dried over sodium sulphate. A pale yellow solid is isolated  
15 (1.51 g; yield of 90.9%) after evaporation under vacuum of the solvents.

NMR  $^1\text{H}$  (DMSO- $d_6$ , 400 MHz)  $\delta$ : 13.28 (broad s, 1H); 7.16 (s, 1H); 6.69 (broad s, 1H); 6.65 (s, 1H); 6.54 (s, 2H); 4.17 (t, 2H,  $J = 7.2$  Hz); 2.89 (q, 2H,  $J = 6.4$  Hz); 2.22 (s, 6H); 1.63 (q, 2H,  $J = 6.8$  Hz); 1.41 (m, 2H); 1.36 (s, 9H); 1.25 (m, 2H). MS/LC:  $m/z = 434.27$  (M+H) $^+$

Preparation 27

*tert*-butyl 5-[(2*Z*)-2-[(3,5-dimethylphenyl)imino]-4-[[[(1-phenylpropyl)amino]carbonyl]-1,3-thiazol-3(2*H*)-yl]pentylcarbamate  
(C<sub>31</sub>H<sub>42</sub>N<sub>4</sub>O<sub>3</sub>S; MM = 550.76)



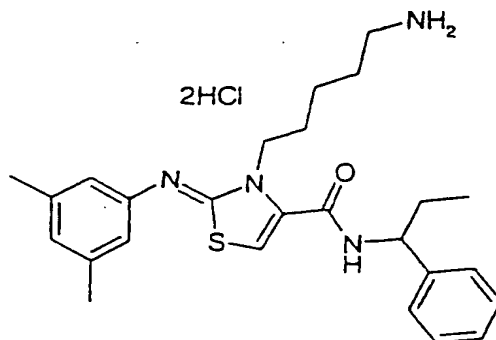
5 600 mg (1.38 mmol) of carboxylic acid of Preparation 26 are activated beforehand with  
888 mg (2.76 mmol; 2 equiv.) of TBTU in 10 ml of anhydrous dimethylformamide for  
one hour. 410  $\mu$ l (2.76 mmol; 2 equiv.) of  $\alpha$ -ethylbenzylamine is then added and the  
mixture is agitated at ambient temperature overnight. After evaporation of the  
dimethylformamide, the crude residue is purified by flash chromatography on silica gel  
10 (eluent: ethyl acetate / heptane 4:6) in order to produce a white solid (498 mg; yield of  
65.5%).

NMR <sup>1</sup>H (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$ : 9.00 (d, 1H, J = 8.4 Hz); 7.36-7.30 (m, 4H); 7.25-  
7.21 (m, 1H); 6.72 (t, 1H, J = 5.4 Hz); 6.67 (s, 1H); 6.63 (s, 1H); 6.53 (s, 2H); 4.77 (q,  
1H, J = 8.8 Hz); 3.95 (m, 2H); 2.84 (q, 2H, J = 6 Hz); 2.21 (s, 6H); 1.74 (m, 2H); 1.51  
15 (m, 2H); 1.36 (s, 9H); 1.31 (q, 2H, J = 7.2 Hz); 1.13 (m, 2H); 0.89 (t, 3H, J = 7.2 Hz).  
MS/LC: m/z = 551.44 (M+H)<sup>+</sup>.

Example 2826

(2Z)-3-(5-aminopentyl)-2-[(3,5-dimethylphenyl)imino]-N-(1-phenylpropyl)-2,3-dihydro-1,3-thiazole-4-carboxamide dihydrochloride

(C<sub>26</sub>H<sub>34</sub>N<sub>4</sub>OS.2HCl; MM = 523.57)



- 5 300 mg (0.54 mmol) of *tert*-butyl 5-[(2Z)-2-[(3,5-dimethylphenyl)imino]-4-[[[(1-phenylpropyl)amino]carbonyl]-1,3-thiazol-3(2H)-yl]pentylcarbamate is dissolved in 15 ml of ethyl acetate. After bubbling anhydrous hydrogen chloride through the reaction medium for one hour at ambient temperature, the corresponding dihydrochloride salt precipitates. It is recovered by filtration and washed with diethyl ether in order to produce a white solid (268 mg; yield of 94.8%).
- 10

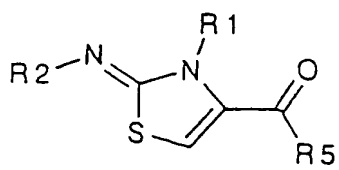
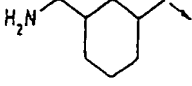
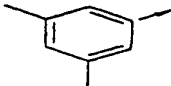
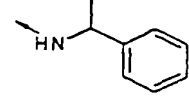
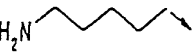
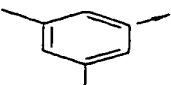
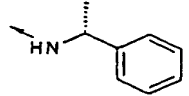
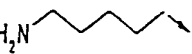
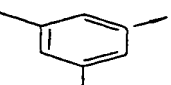
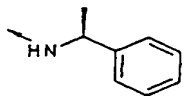
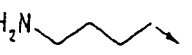
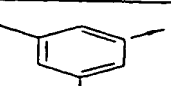
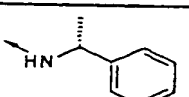
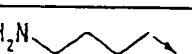
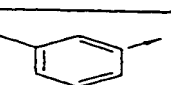
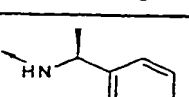
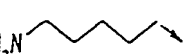
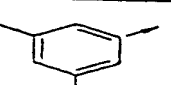
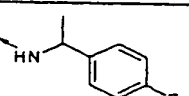

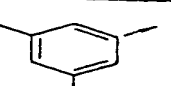
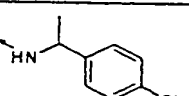
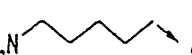
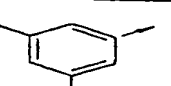
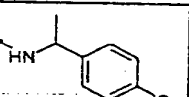

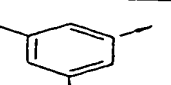
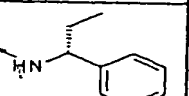
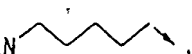
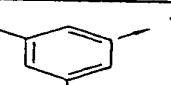
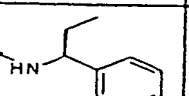
NMR <sup>1</sup>H (DMSO-*d*<sub>6</sub>, 400 MHz): 9.48 (broad s, 1H); 8.03 (broad s, 3H); 7.39-7.32 (m, 5H); 7.25 (t, 1H, J = 7.2 Hz); 7.00 (m, 3H); 4.80 (q, 1H, J = 8.4 Hz); 4.33 (broad s, 2H); 2.70 (q, 2H, J = 6.8 Hz); 2.29 (s, 6H); 1.77 (m, 2H); 1.65 (m, 2H); 1.52 (m, 2H); 1.27 (m, 2H); 0.89 (t, 3H, J = 7.2 Hz).

- 15 MS/LC: m/z = 451.35 (M+H)<sup>+</sup>.

According to method G, a series of compounds can be synthesized which include:

- the R1 and R2 groups already described for method A; and
- the R5 groups already described for method C.

- 20 In particular, the compounds shown in the table below have been synthesised using method G.

<div style="text-align: center;">  <p>2HCl</p> </div>						
Ex.	R1	R2	R5	Purity (%)	rt (min)	[M+H] <sup>+</sup>
2827				69 + 27	4.57 + 4.73	477.33
2828				98	4.36	437.29
2829				98	4.37	437.33
2830				98	3.72	423.37
2831				99	3.73	423.37
2832				99	4.07	455.32
2833				99	4.29	471.32
2834				98	4.33	515.24
2835				99	3.87	451.34
2836				99	3.88	451.34



## PHARMACOLOGICAL PROPERTIES OF THE PRODUCTS OF THE INVENTION

The compounds of the present invention can and have been tested as regards their affinity for different sub-types of somatostatin receptors according to the procedures described below.

### *Study of the affinity for the sub-types of human somatostatin receptors:*

The affinity of a compound of the invention on sub-types of human somatostatin receptors 1 to 5 (sst<sub>1</sub>, sst<sub>2</sub>, sst<sub>3</sub>, sst<sub>4</sub> and sst<sub>5</sub>, respectively) is determined by measurement of the inhibition of the bond of [<sup>125</sup>I-Tyr<sup>11</sup>]SRIF-14 to transfected CHO-K1 cells.

The gene of the sst<sub>1</sub> receptor of human somatostatin was cloned in the form of a genomic fragment. A segment *Pst*I-*Xmn*I of 1.5 Kb containing 100 bp of the non transcribed 5' region, 1.17 Kb of the coding region in totality, and 230 bp of the non transcribed 3' region is modified by the addition of the linker *Bgl*II. The resulting DNA fragment is subcloned in the *Bam*HI site of a pCMV-81 in order to produce the expression plasmid in mammals (provided by Dr. Graeme Bell, Univ. Chicago). A cloned cell line expressing in a stable fashion the sst<sub>1</sub> receptor is obtained by transfection in CHO-K1 cells (ATCC) using the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) is included as selection marker. Cloned cell lines were selected in an RPMI 1640 medium containing 0.5 mg/ml of G418 (Gibco), followed by circular cloning and multiplication in culture.

The gene of the sst<sub>2</sub> receptor of human somatostatin, isolated in the form of a genomic fragment of DNA of 1.7 Kb *Bam*HI-*Hind*III and subcloned in a plasmid vector pGEM3Z (Promega), was provided by Dr. G. Bell (Univ. of Chicago). The expression vector of the mammalian cells is constructed by inserting the *Bam*HI-*Hind*III fragment of 1.7 Kb in endonuclease restriction sites compatible with the plasmid pCMV5. A cloned cell line is obtained by transfection in CHO-K1 cells using the calcium phosphate co-precipitation method. The plasmid pRSV-neo is included as selection marker.

The sst<sub>3</sub> receptor is isolated as a genomic fragment, and the complete coding sequence is contained in a *Bam*HI-*Hind*III fragment of 2.4 Kb.

mammals, pCMV-h3, is constructed by insertion of the *NcoI-HindIII* fragment of 2.0 Kb in the *EcoRI* site of the vector pCMV after modification of the terminations and addition of *EcoRI* linkers. A cloned cell line expressing in a stable fashion the *sst3* receptor is obtained by transfection in CHO-K1 cells (ATCC) by the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) is included as selection marker. Cloned cell lines were selected in an RPMI 1640 medium containing 0.5 mg/ml of G418 (Gibco), followed by circular cloning and multiplication in culture.

The expression plasmid of the human *sst4* receptor, pCMV-HX, was provided by Dr. Graeme Bell (Univ. Chicago). This vector contains the genomic fragment coding for the human *sst4* receptor of 1.4 Kb *NheI-NheI*, 456 bp of the non transcribed 5' region, and 200 bp of the non transcribed 3' region, cloned in the *XbaI/EcoRI* sites of pCMV-HX. A cloned cell line expressing in a stable fashion the *sst4* receptor is obtained by transfection in CHO-K1 (ATCC) cells by the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) is included as selection marker. Cloned cell lines were selected in an RPMI 1640 medium containing 0.5 mg/ml of G418 (Gibco), followed by circular cloning and multiplication in culture.

The gene corresponding to the human *sst5* receptor, obtained by the PCR method using a genomic  $\lambda$  clone as probe, was provided by Dr. Graeme Bell (Univ. Chicago). The resulting PCR fragment of 1.2 Kb contains 21 base pairs of the non transcribed 5' region, the coding region in totality, and 55 bp of the non transcribed 3' region. The clone is inserted in an *EcoRI* site of the plasmid pBSSK(+). The insert is recovered in the form of a *HindIII-XbaI* fragment of 1.2 Kb for subcloning in an expression vector in mammals, pCVM5. A cloned cell line expressing in a stable fashion the *sst5* receptor is obtained by transfection in CHO-K1 cells (ATCC) by the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) is included as selection marker. Cloned cell lines were selected in an RPMI 1640 medium containing 0.5 mg/ml of G418 (Gibco), followed by circular cloning and multiplication in culture.

The CHO-K1 cells which express in a stable fashion the human *sst* receptors are cultured in an RPMI 1640 medium containing 10% of foetal calf serum and 0.4 mg/ml of geneticin. The cells are collected with EDTA at 0.5 mM and centrifuged at 500 g for approximately 5 minutes at approximately 4°C. The pellet is resuspended in a Tris 50 mM buffer at pH 7.4 and centrifuged twice at 500 g for approximately 5 minutes at approximately 4°C. The cells are lysed by sonication then centrifuged at 39000 g for approximately 10 minutes at 4°C. The pellet is resuspended in the same buffer and centrifuged at 50000 g for approximately 10 minutes at approximately 4°C and the membranes in the pellet obtained are stored at -80°C.

The competitive inhibition experiments of the bond with [ $^{125}\text{I-Tyr}^{11}$ ]SRIF-14 are carried out in duplicate in 96-well polypropylene plates. The cell membranes (10  $\mu\text{g}$  protein/well) are incubated with [ $^{125}\text{I-Tyr}^{11}$ ]SRIF-14 (0.05 nM) for approximately 60 min. at approximately 37 °C in a HEPES 50 mM buffer (pH 7.4) containing BSA 0.2 %,  $\text{MgCl}_2$  5 mM, Trasylol 200 KIU/ml, bacitracin 0.02 mg/ml and phenylmethanesulphonyl fluoride 0.02 mg/ml.

The bound [ $^{125}\text{I-Tyr}^{11}$ ]SRIF-14 is separated from the free [ $^{125}\text{I-Tyr}^{11}$ ]SRIF-14 by immediate filtration through GF/C glass fibre filter plates (Unifilter, Packard) pre-impregnated with 0.1 % of polyethylenimine (P.E.I.), using a Filtermate 196 (Packard).

10 The filters are washed with 50 mM HEPES buffer at approximately 0-4 °C for approximately 4 seconds and their radioactivity is determined using a counter (Packard Top Count).

The specific bond is obtained by subtracting the non-specific bond (determined in the presence of 0.1  $\mu\text{M}$  of SRIF-14) from the total bond. The data relative to the bond is

15 analyzed by computer-aided non-linear regression analysis (MDL) and the values of the inhibition constants ( $K_i$ ) are determined.

Determination of the agonist or antagonist character of a compound of the present invention is carried out using the test described below.

*Functional test: Inhibition of production of intracellular cAMP:*

CHO-K1 cells expressing the sub-types of human somatostatin receptors (SRIF-14) are cultured in 24-well plates in an RPMI 1640 medium with 10% of foetal calf serum and 0.4 mg/ml of geneticin. The medium is changed the day preceding the experiment.

- 5 The cells at a rate of  $10^5$  cells/well are washed twice with 0.5 ml of new RPMI medium comprising 0.2 % BSA completed by 0.5 mM of 3-isobutyl-1-methylxanthine (IBMX) and incubated for approximately 5 minutes at approximately 37 °C.

☐ The production of cyclic AMP is stimulated by the addition of 1 mM of forskolin (FSK) for 15-30 minutes at approximately 37 °C.

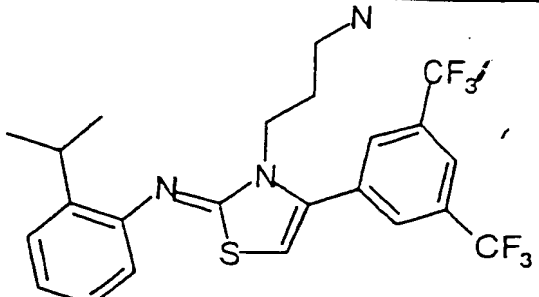
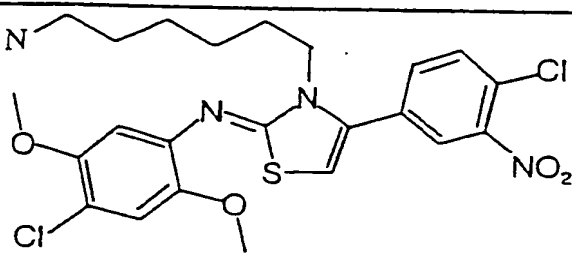
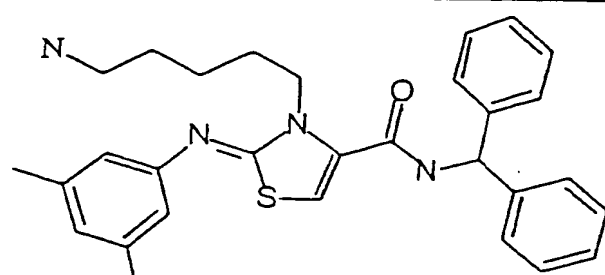
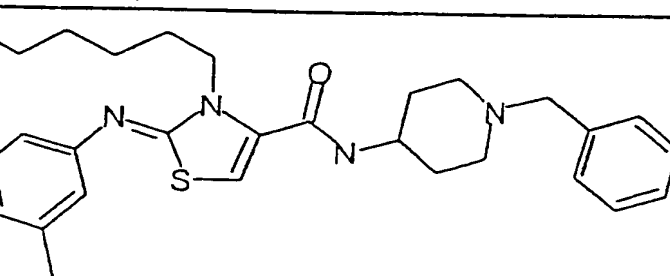
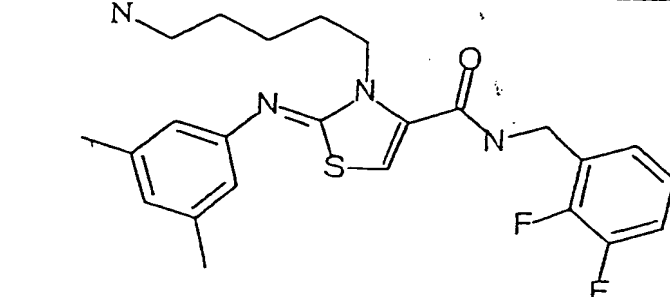
- 10 ☐ The inhibitory effect of the somatostatin of an agonist compound is measured by the simultaneous addition of FSK (1 $\mu$ M) , SRIF-14 ( $10^{-12}$  M to  $10^{-6}$  M) and of the compound to be tested ( $10^{-10}$  M to  $10^{-5}$  M).

- ☐ The antagonist effect of a compound is measured by the simultaneous addition of FSK (1 $\mu$ M), SRIF-14 (1 to 10 nM) and of the compound to be tested ( $10^{-10}$  M to  $10^{-5}$  M).
- 15

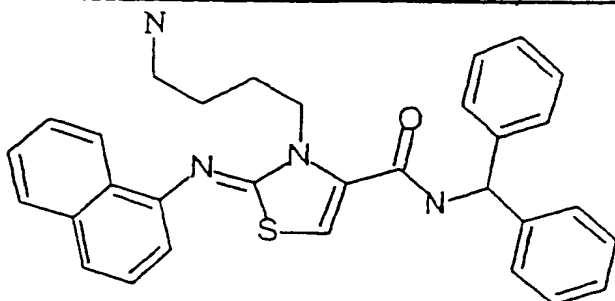
The reaction medium is eliminated and 200 ml of 0.1 N HCl is added. The quantity of cAMP is measured by a radioimmunological test (FlashPlate SMP001A kit, New England Nuclear).

*Results:*

- 20 The tests carried out according to the protocols described above have demonstrated that the products of general formula (I) defined in the present Application have a good affinity for at least one of the sub-types of somatostatin receptors, the inhibition constant  $K_i$  being lower than micromolar for certain exemplified compounds, and in particular for the products shown in the table below.

	Formula of compound	K <sub>i</sub> (nM)
5		< 200
10		< 200
15		< 200
20		< 200
25		< 200

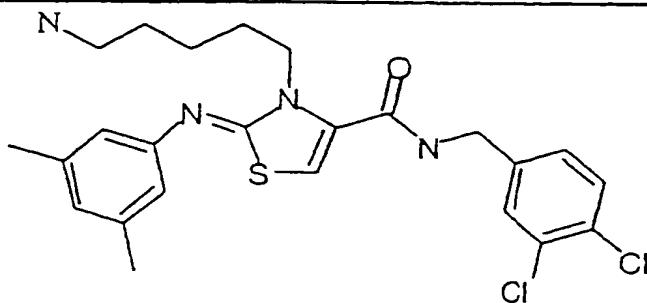
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K<sub>i</sub> (nM)

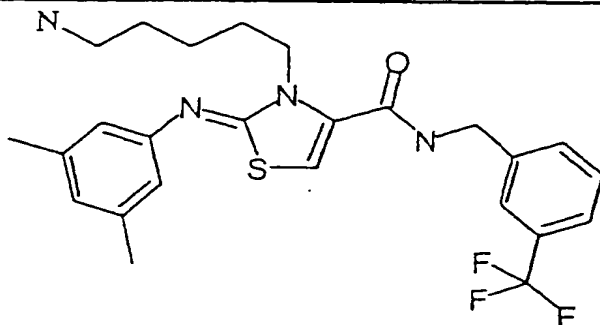
< 200

10



< 200

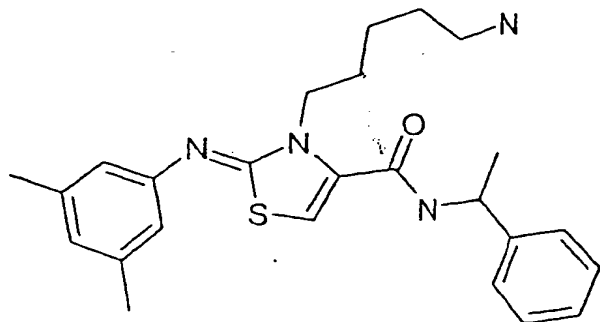
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< 200

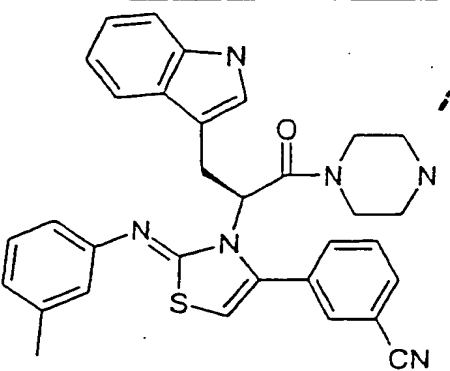
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30

5

	<p>&lt; 200</p>
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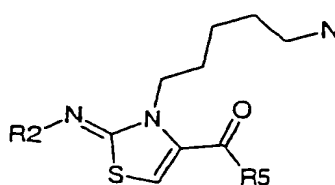
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In addition to the compounds in the above tables, each of the compounds of Examples 2827 to 2836 also has a  $K_i$  constant lower than 200 nM.

# Claims

1. Compound characterized in that it corresponds:

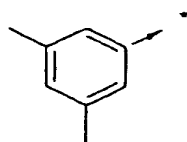
- to the formula



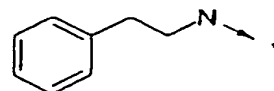
(i)

in which:

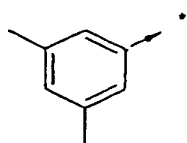
- R2 represents the radical,



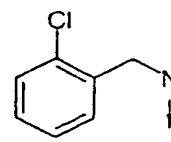
radical and R5 represents the



- R2 represents the

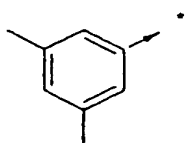


radical and R5 represents the

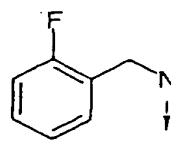


radical,

- R2 represents the

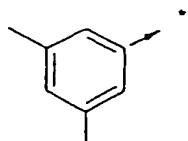


radical and R5 represents the

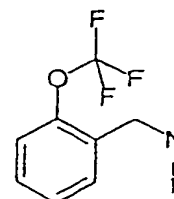


radical,

- R2 represents the radical,



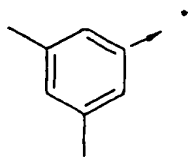
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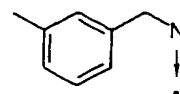


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- R2 represents the



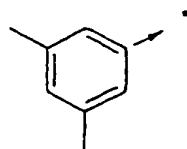
radical and R5 represents the



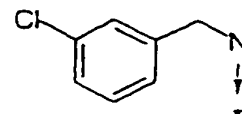
radical,

10

- R2 represents the  
radical,

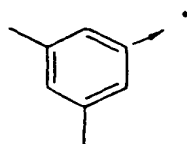


radical and R5 represents the

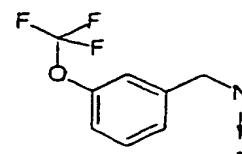


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- R2 represents the  
radical,

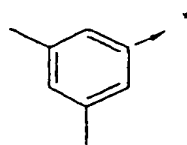


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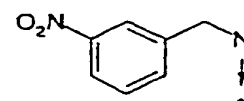


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- R2 represents the  
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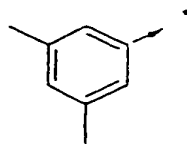


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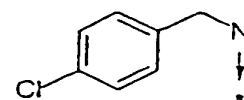


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- R2 represents the  
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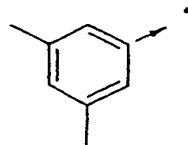


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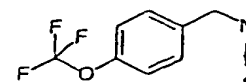


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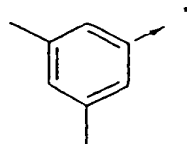


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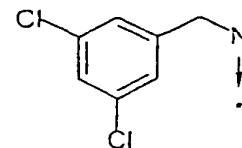


35

- R2 represents the  
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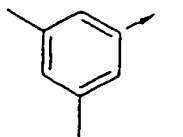


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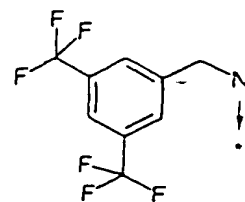


5

- R2 represents the radical,

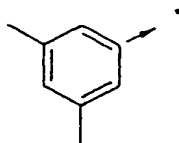


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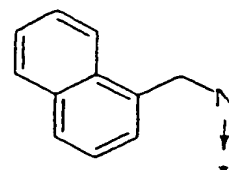


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- R2 represents the radical,

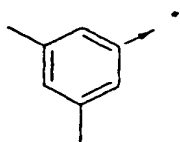


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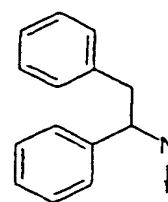


15

- R2 represents the



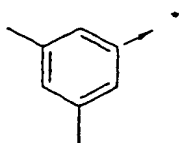
radical and R5 represents the



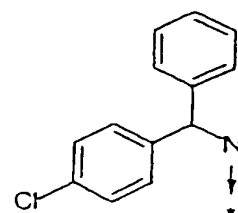
radical,

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- R2 represents the radical,



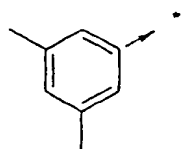
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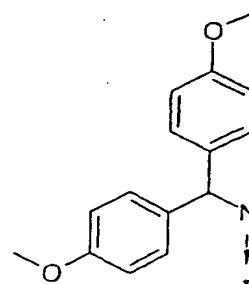
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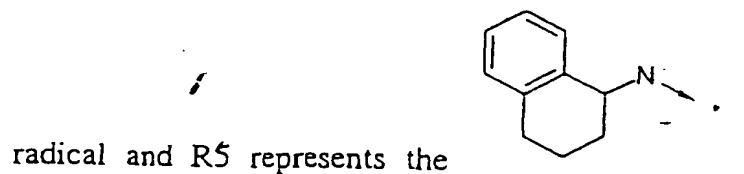
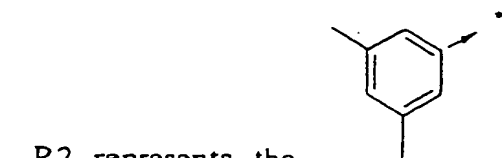
- R2 represents the radical,



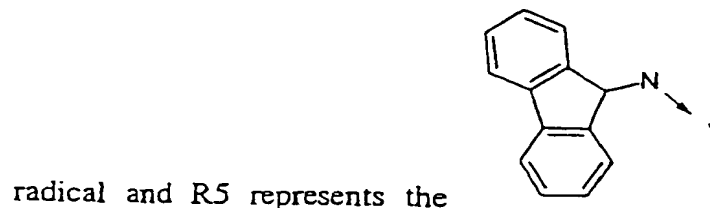
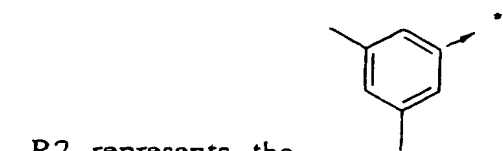
radical and R5 represents the



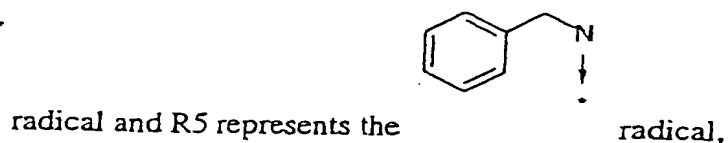
35



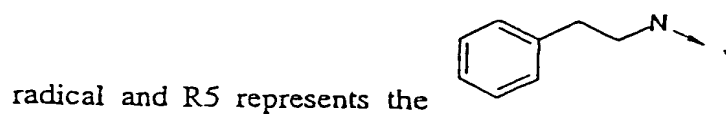
5



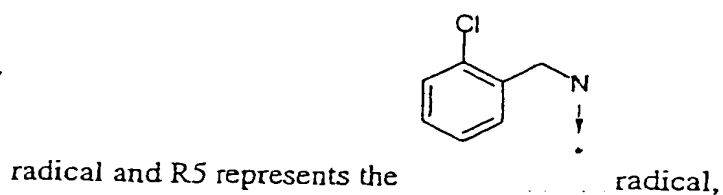
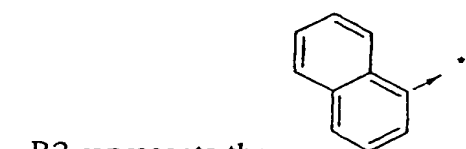
10



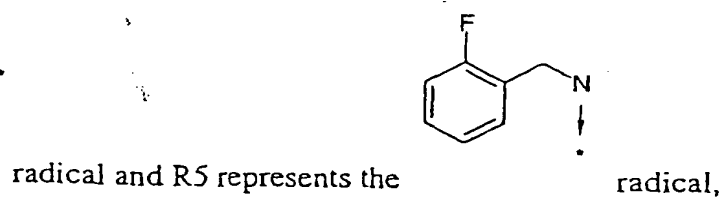
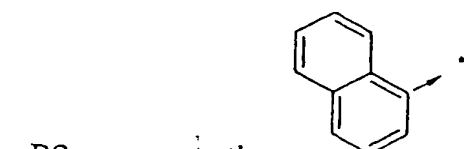
15



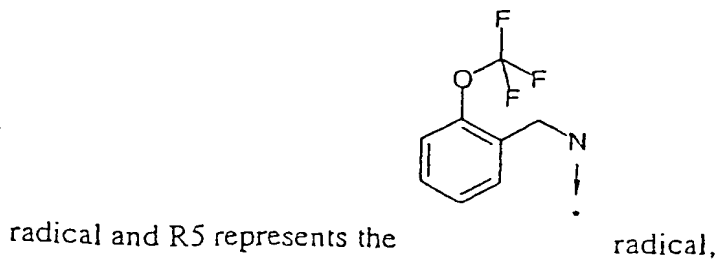
20



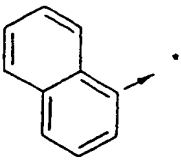
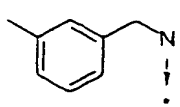
25

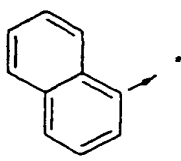
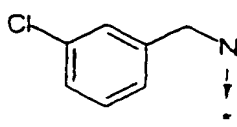


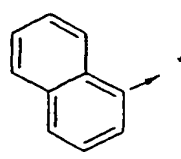
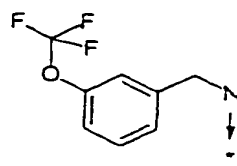
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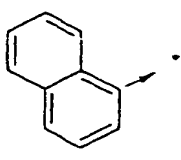
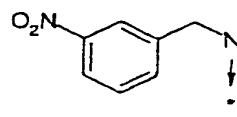


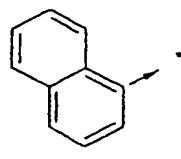
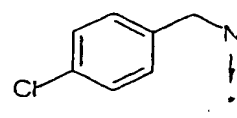
35

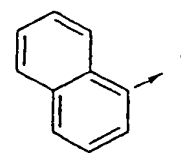
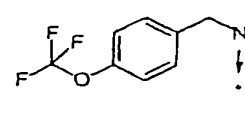
- R2 represents the  radical and R5 represents the  radical,

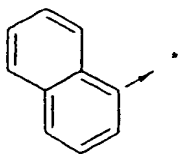
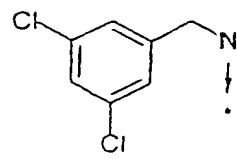
5 - R2 represents the  radical and R5 represents the  radical,

10 - R2 represents the  radical and R5 represents the  radical,

15 - R2 represents the  radical and R5 represents the  radical,

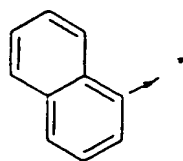
20 - R2 represents the  radical and R5 represents the  radical,

25 - R2 represents the  radical and R5 represents the  radical,

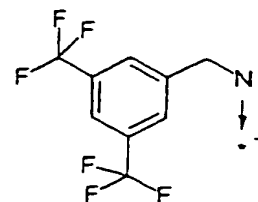
30 - R2 represents the  radical and R5 represents the  radical,

35

- R2 represents the radical,

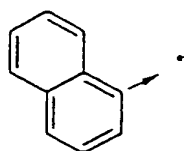


radical and R5 represents the

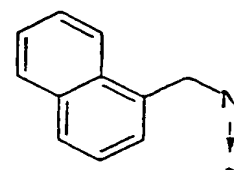


5

- R2 represents the radical,

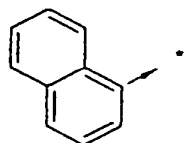


radical and R5 represents the

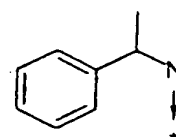


10

- R2 represents the



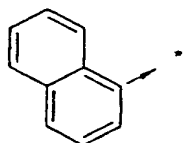
radical and R5 represents the



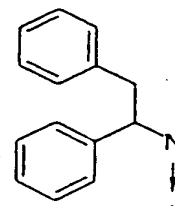
radical,

15

- R2 represents the



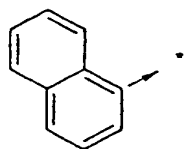
radical and R5 represents the



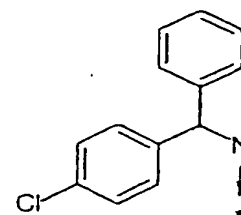
radical,

20

- R2 represents the radical,



radical and R5 represents the



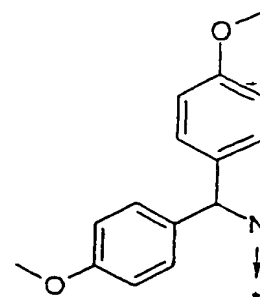
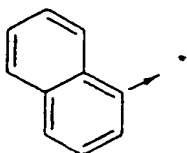
25

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- R2 represents the radical,

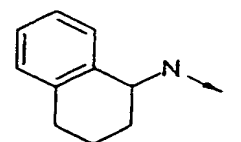
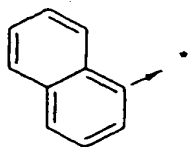
radical and R5 represents the



5

- R2 represents the radical, or finally

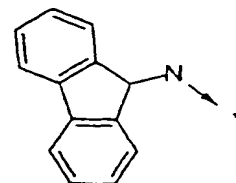
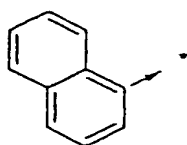
radical and R5 represents the



10

- R2 represents the radical;

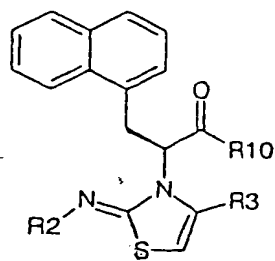
radical and R5 represents the



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• to formula

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
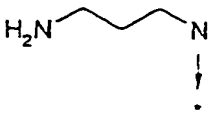
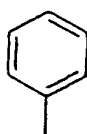


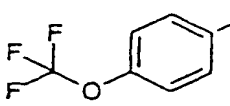
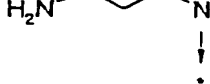

(ii)

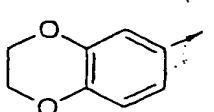
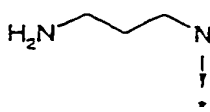
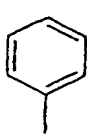
25

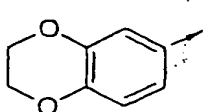
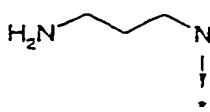
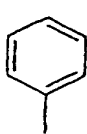
30


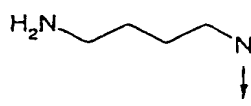
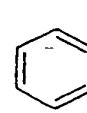
in which:

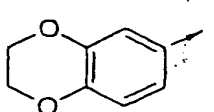
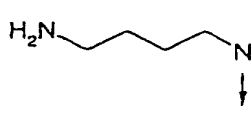
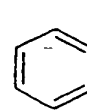
5 - R10 represents  , R2 represents  and R3 represents 


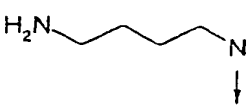
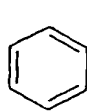
10 - R10 represents  , R2 represents  and R3 represents 

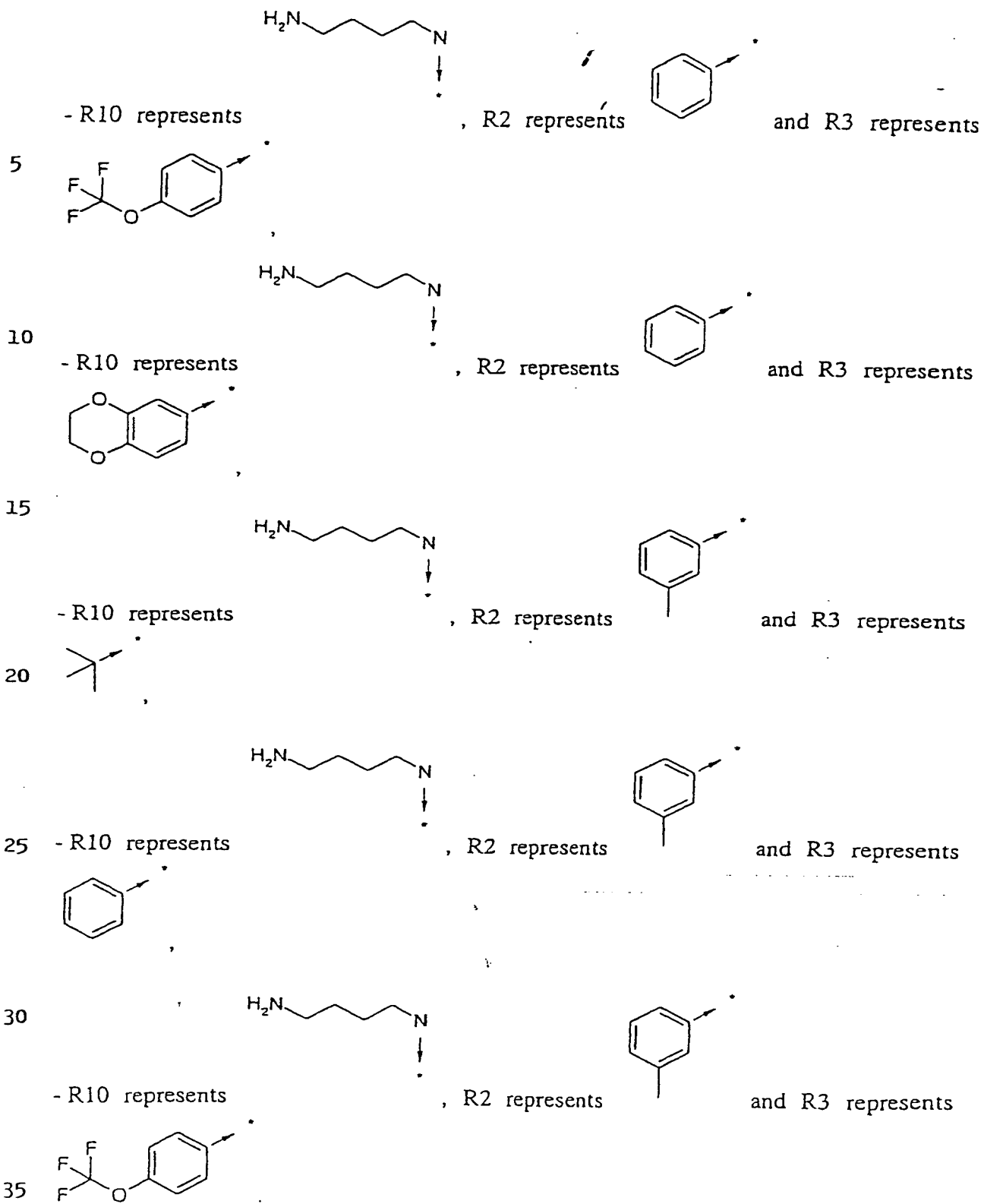
15 - R10 represents  , R2 represents  and R3 represents 

20 - R10 represents  , R2 represents  and R3 represents 

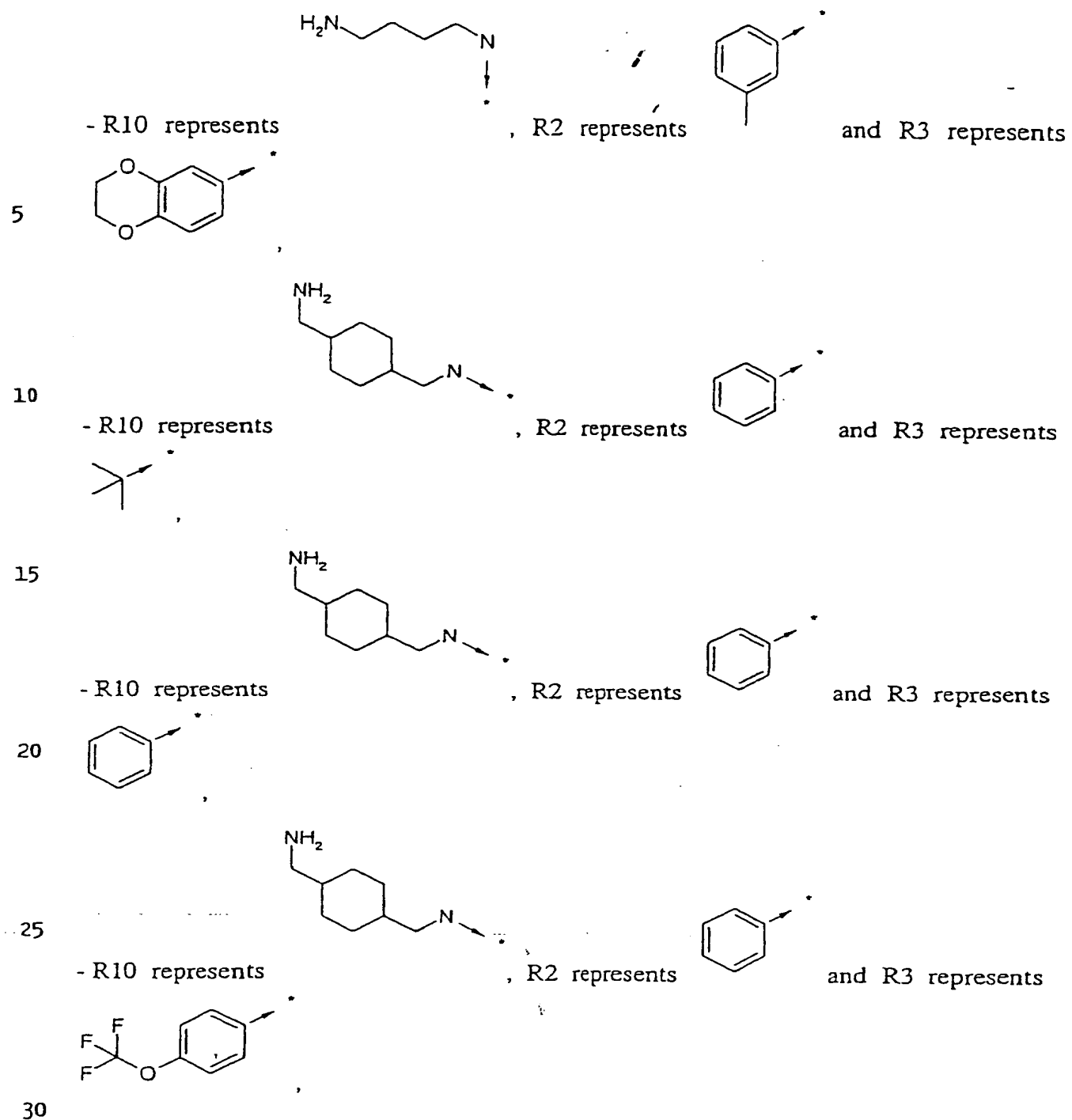
25 - R10 represents  , R2 represents  and R3 represents 

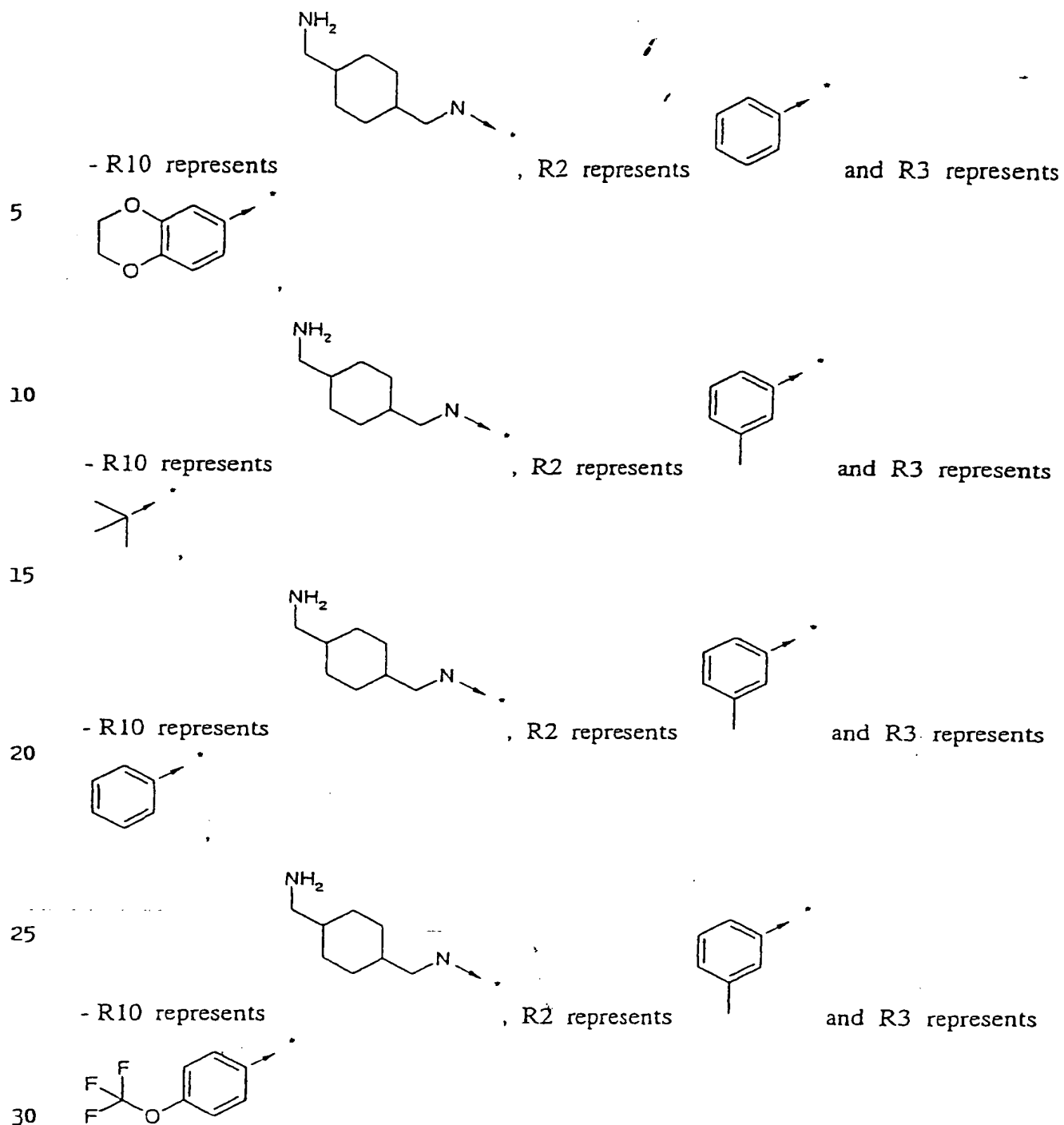
30 - R10 represents  , R2 represents  and R3 represents 

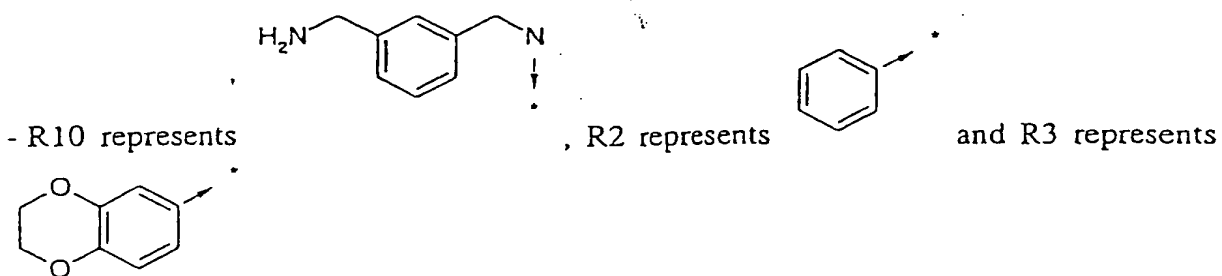
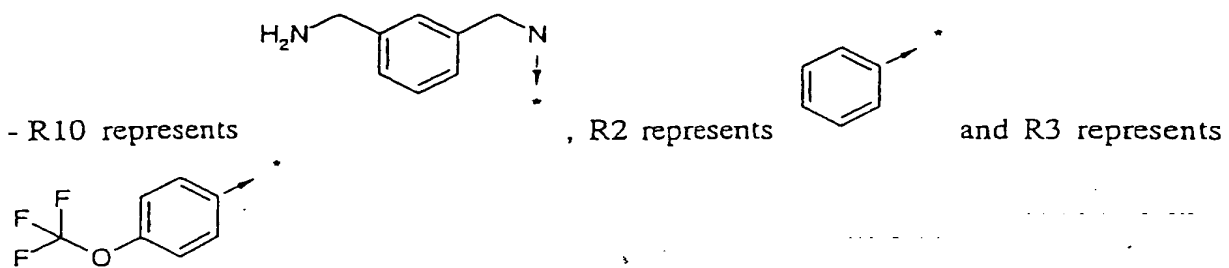
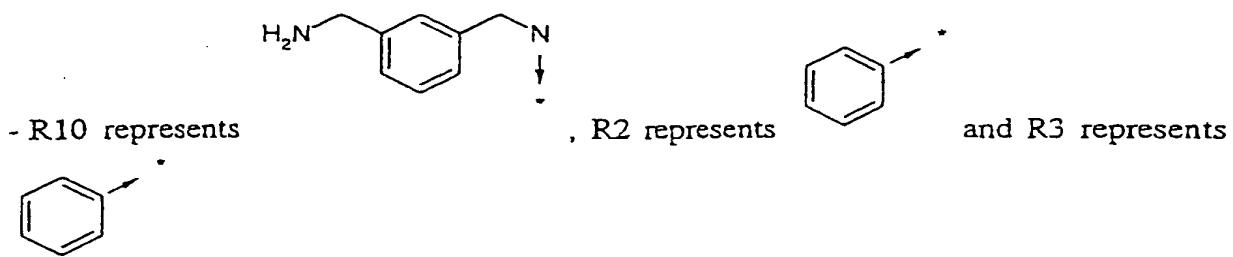
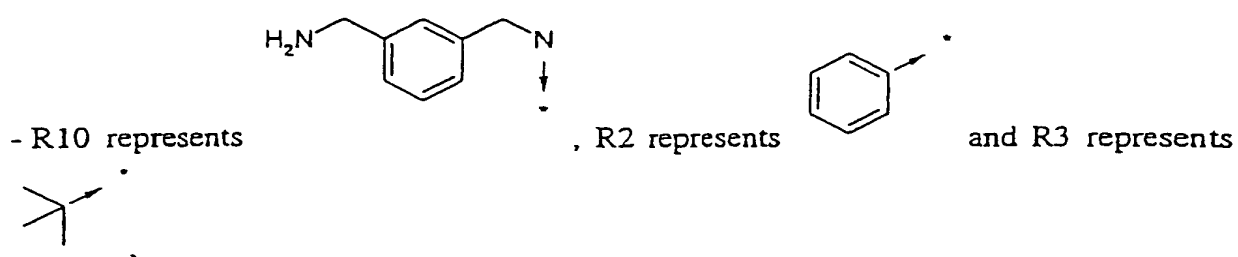
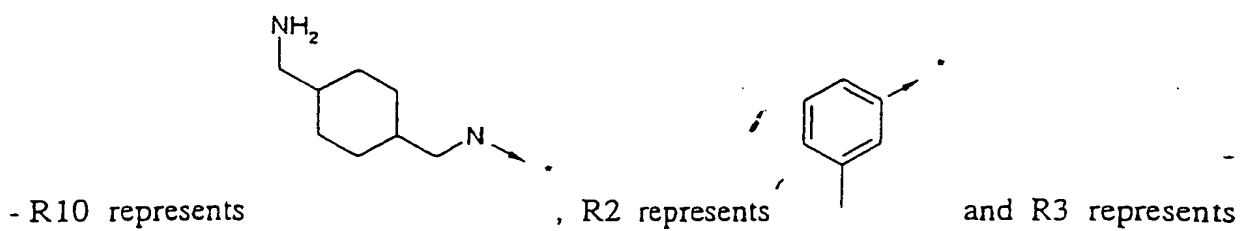
35 - R10 represents  , R2 represents  and R3 represents 



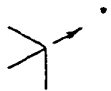




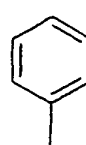




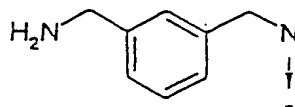
- R10 represents



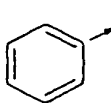
, R2 represents



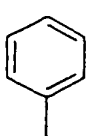
and R3 represents



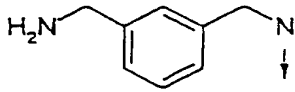
- R10 represents



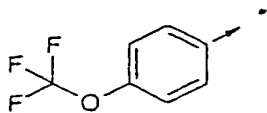
, R2 represents



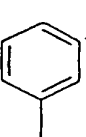
and R3 represents



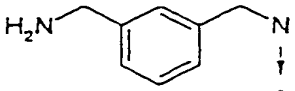
- R10 represents



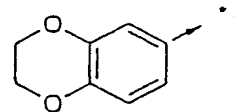
, R2 represents



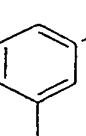
and R3 represents



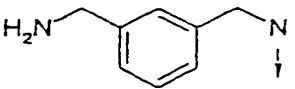
- R10 represents



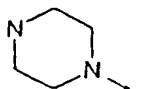
, R2 represents



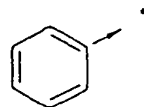
and R3 represents



- R10 represents



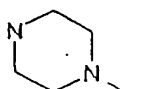
, R2 represents



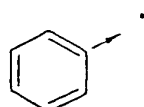
and R3 represents



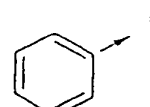
- R10 represents

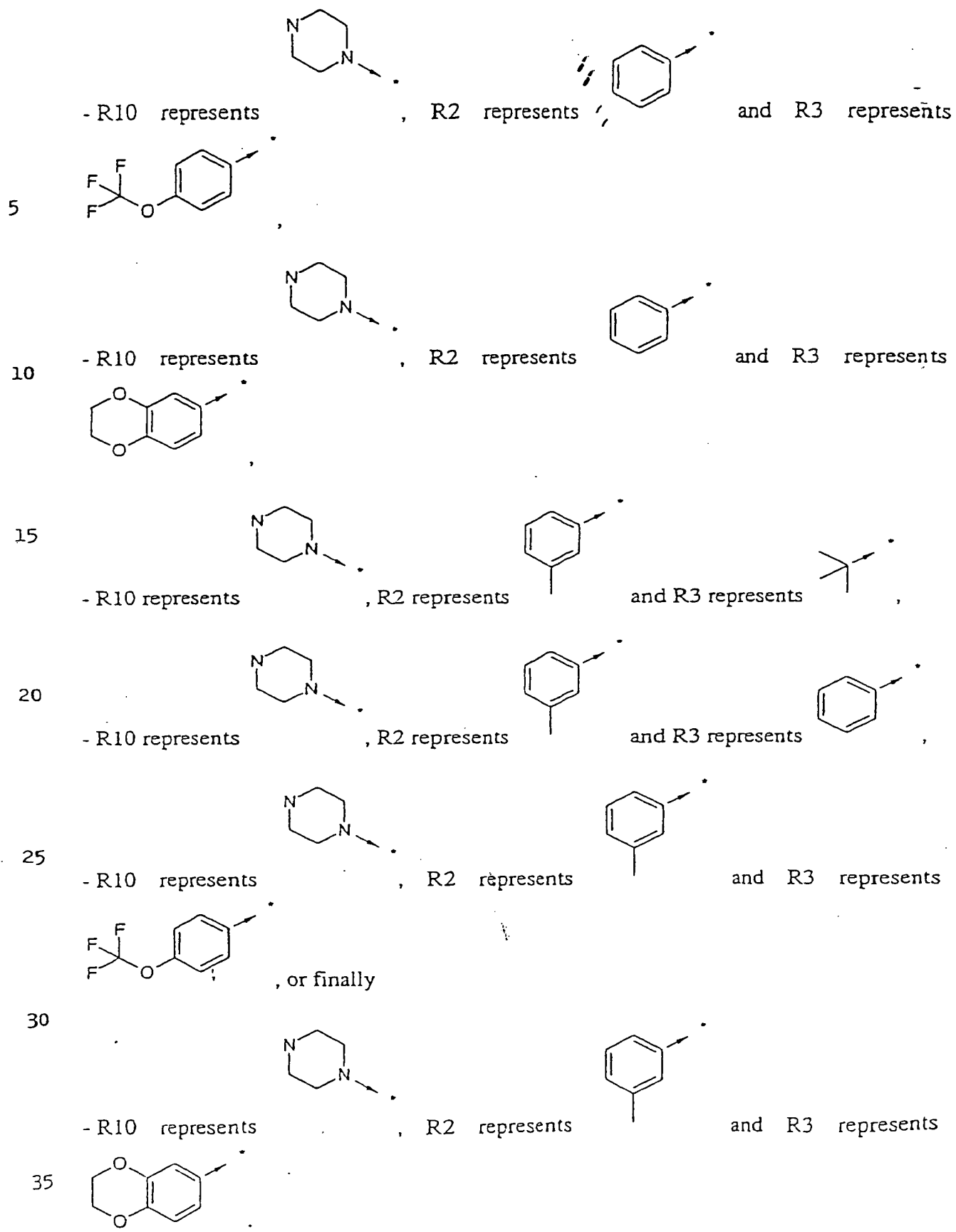


, R2 represents

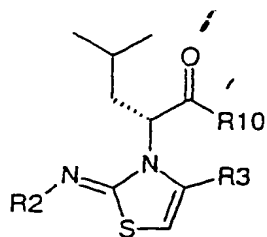


and R3 represents





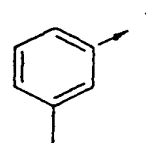
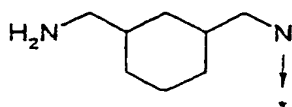
to formula



(iii)

in which:

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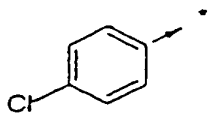


- R10 represents

, R2 represents

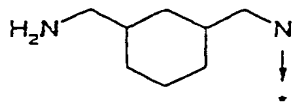
and R3 represents

15

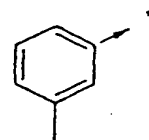


20

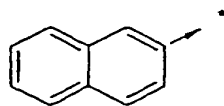
- R10 represents



, R2 represents

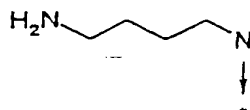


and R3 represents

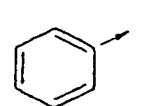


25

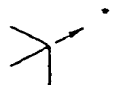
- R10 represents



, R2 represents

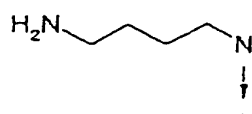


and R3 represents

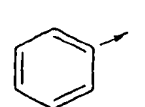


30

- R10 represents

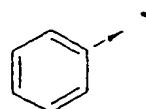


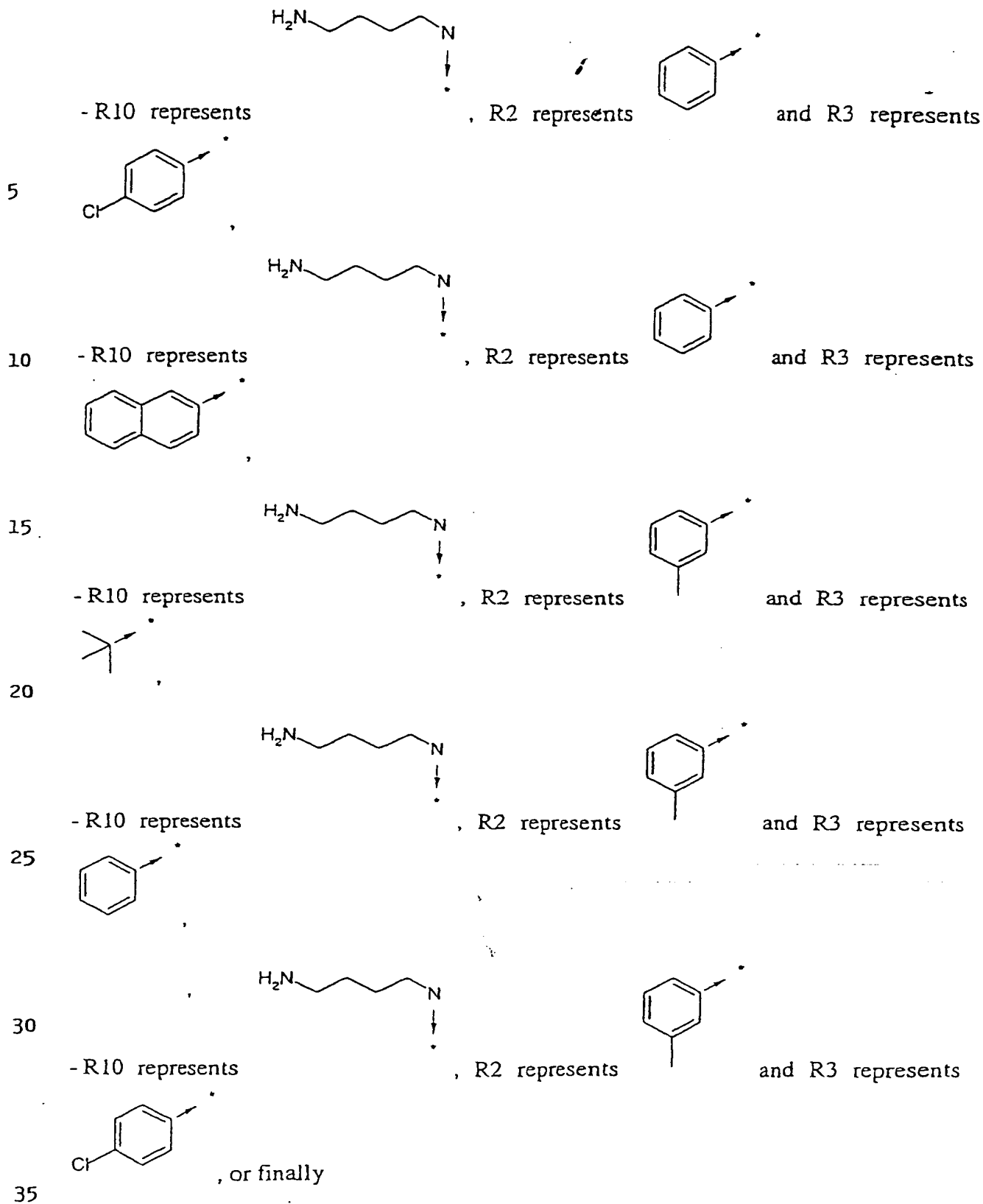
, R2 represents

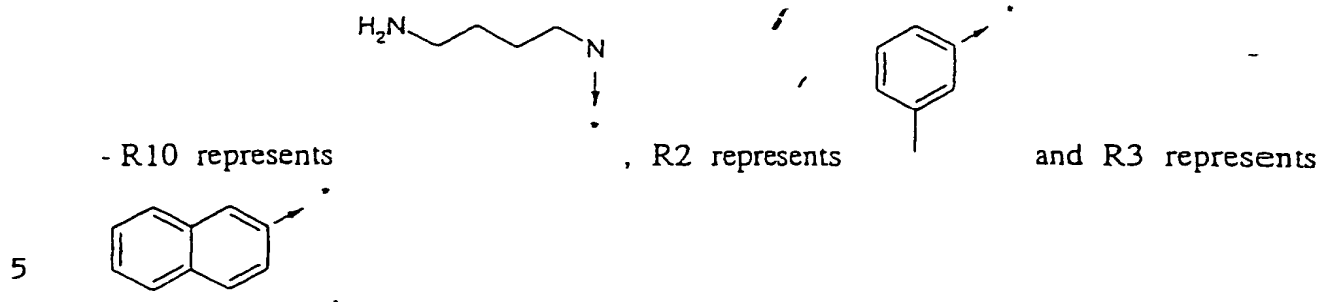


and R3 represents

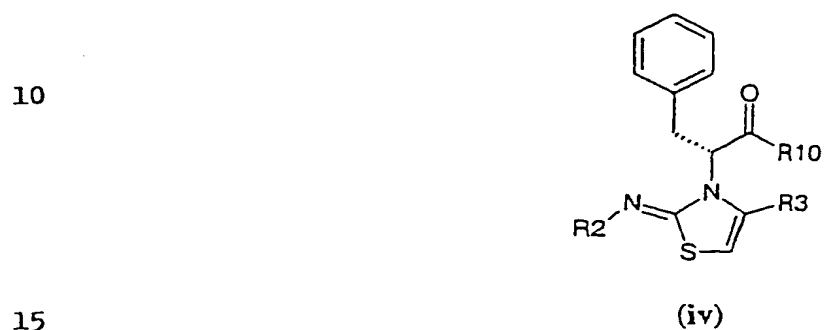
35



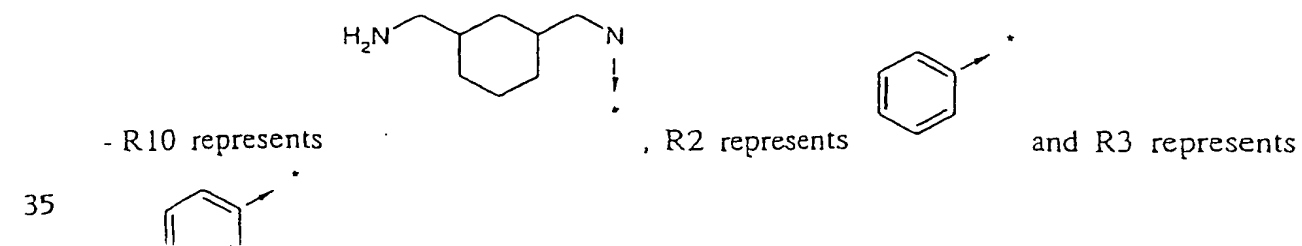
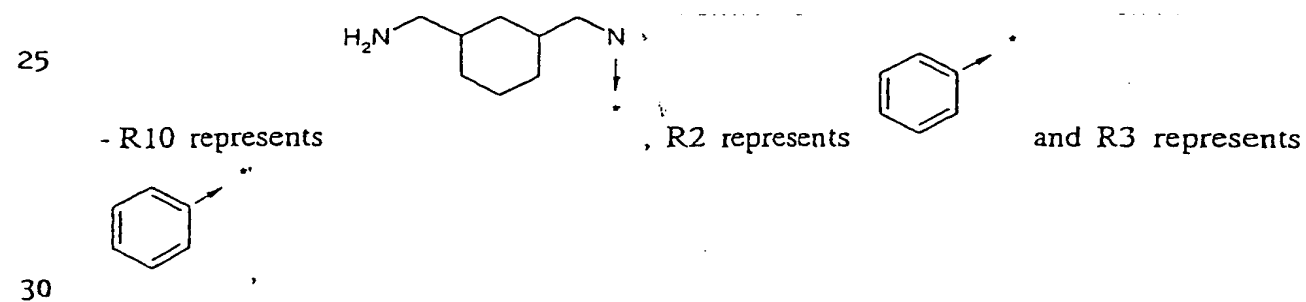
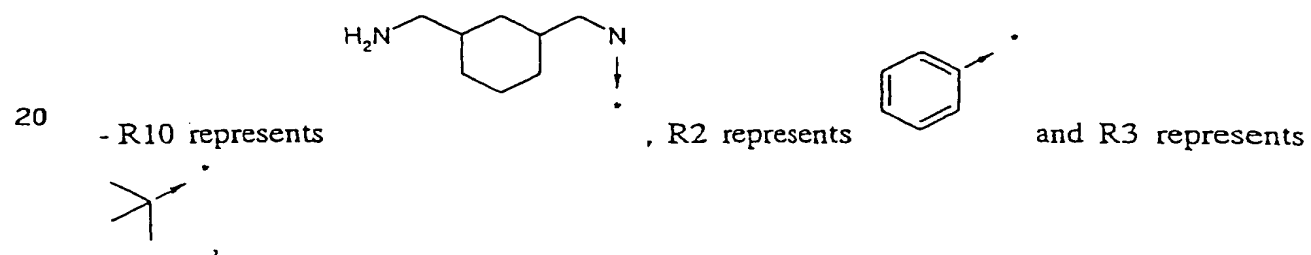




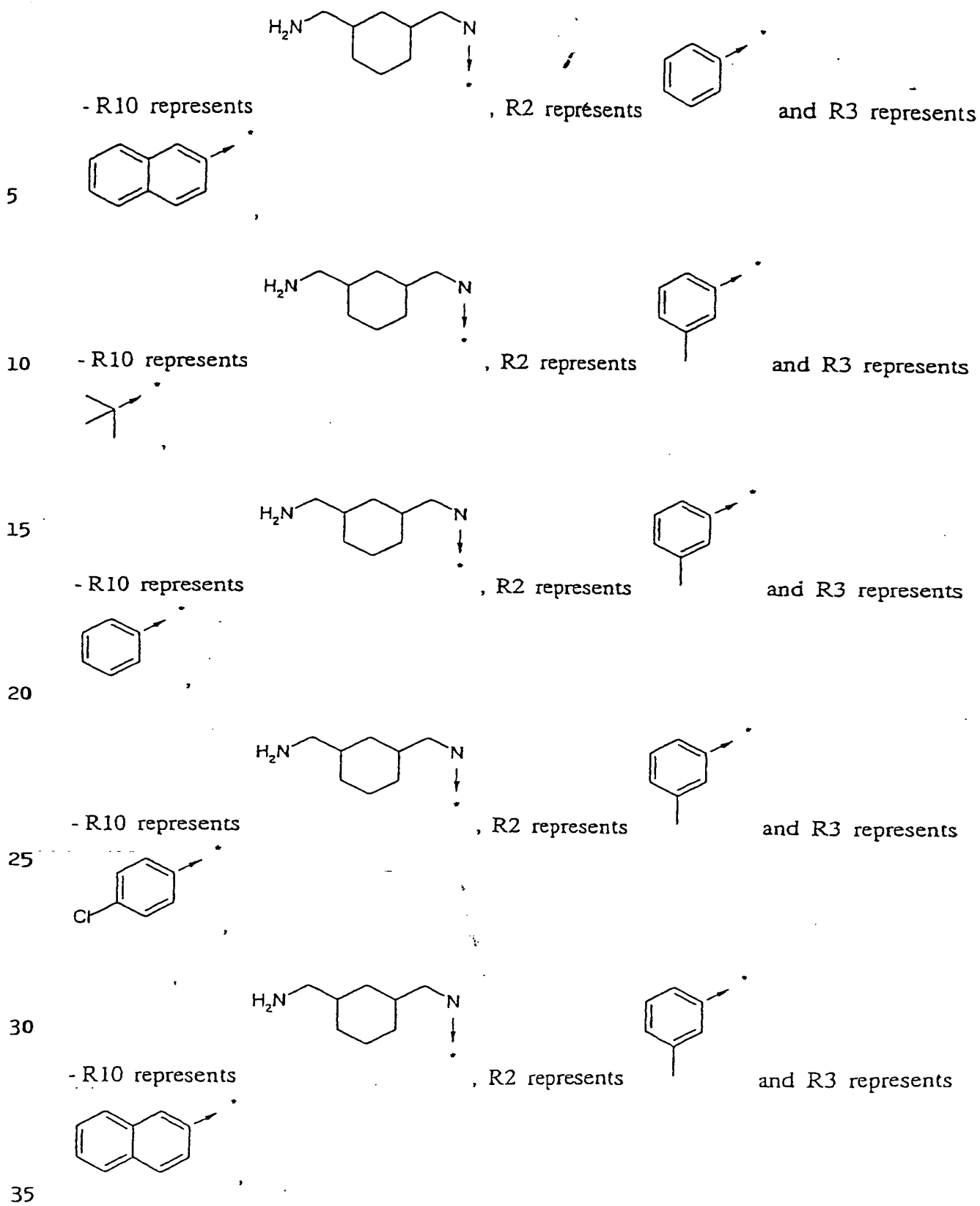
• to formula

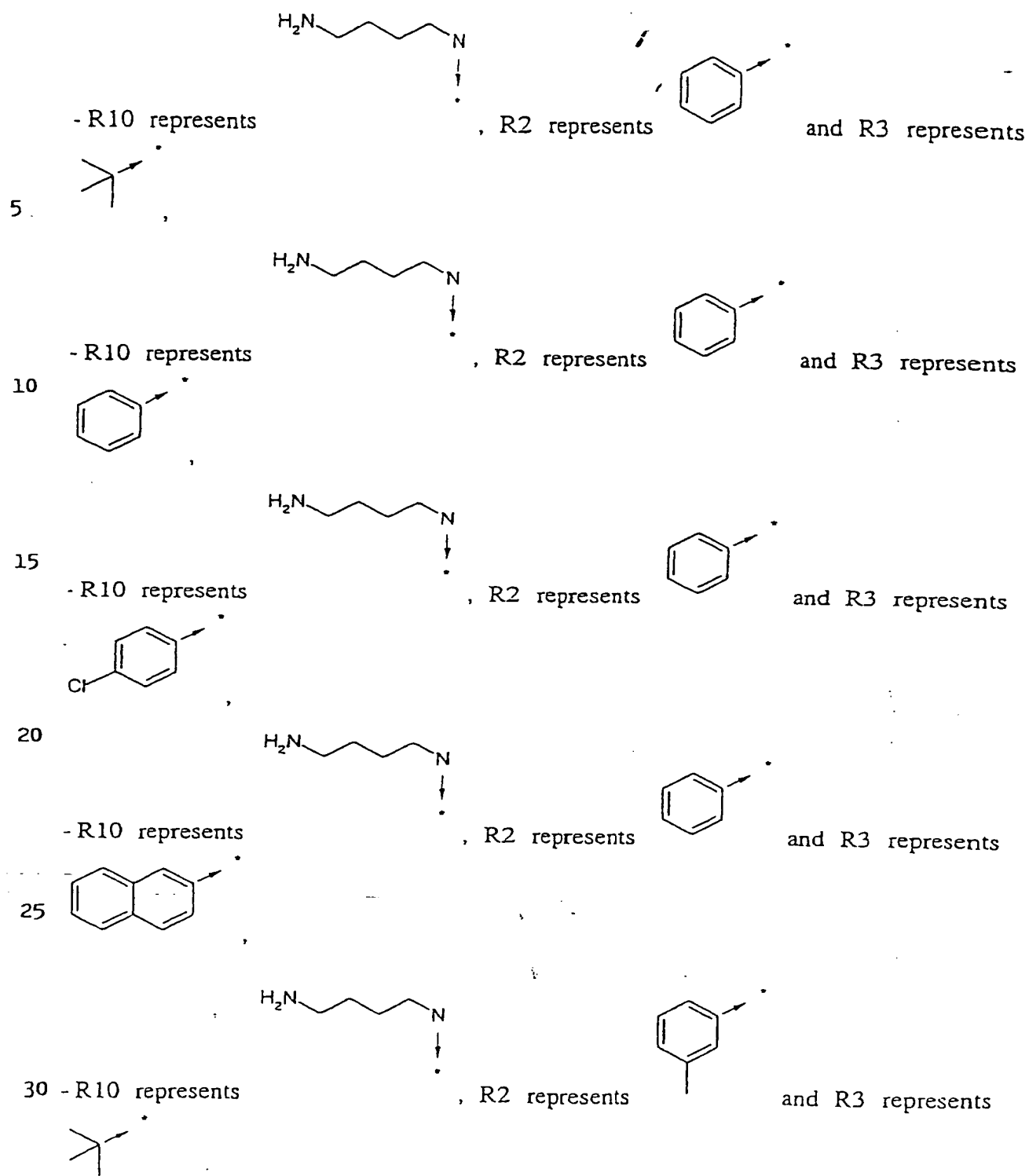


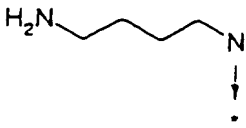
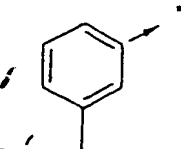
in which:

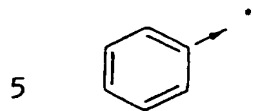


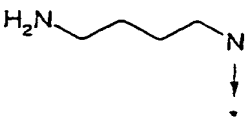
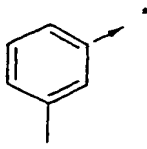


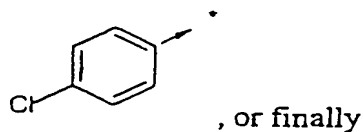


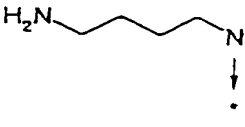
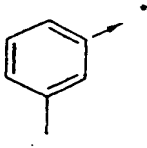


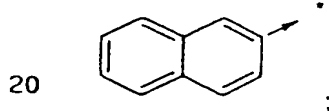
- R10 represents , R2 represents  and R3 represents



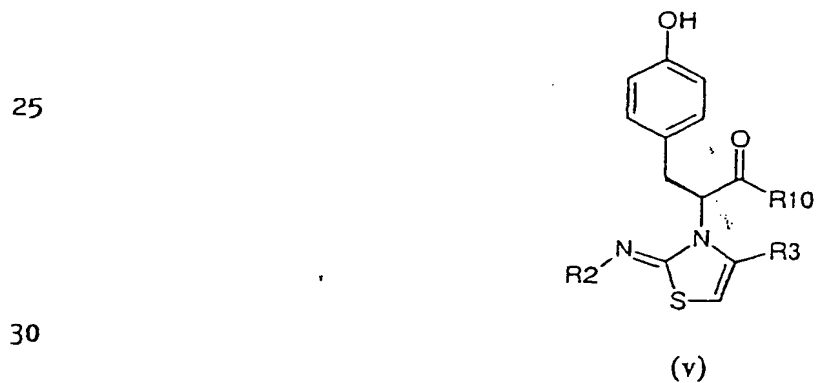
10 - R10 represents , R2 represents  and R3 represents



15 - R10 represents , R2 represents  and R3 represents



• to formula



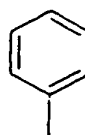
in which:

5

- R10 represents



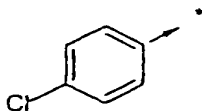
, R2 represents



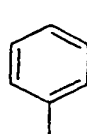
and R3 represents

10

- R10 represents



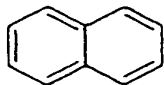
, R2 represents



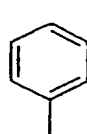
and R3 represents

15

- R10 represents



, R2 represents



and R3 represents

20

25

- R10 represents



, R2 represents



and R3 represents

30

- R10 represents

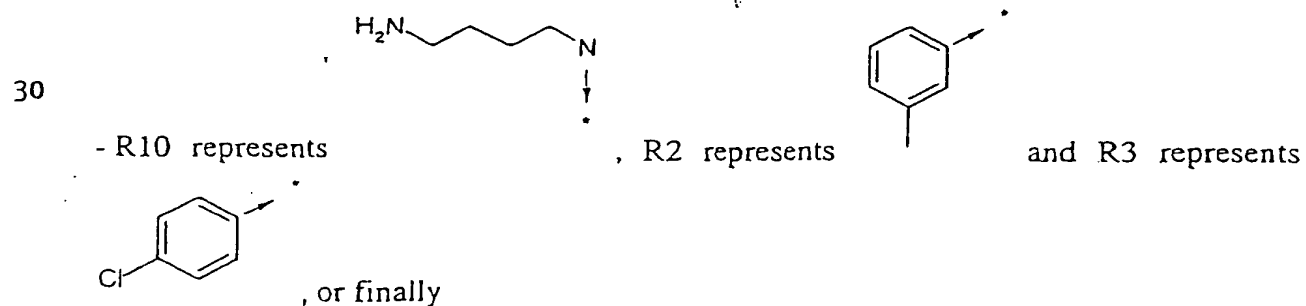
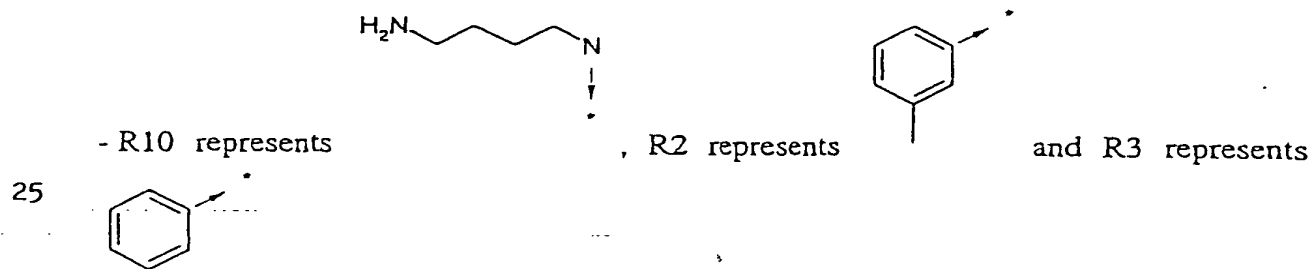
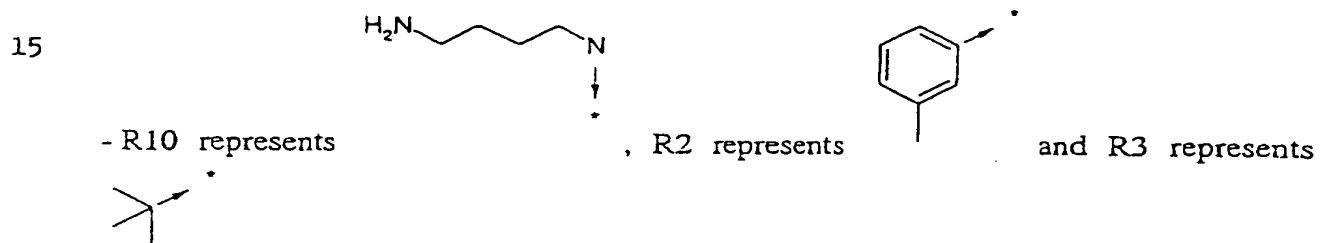
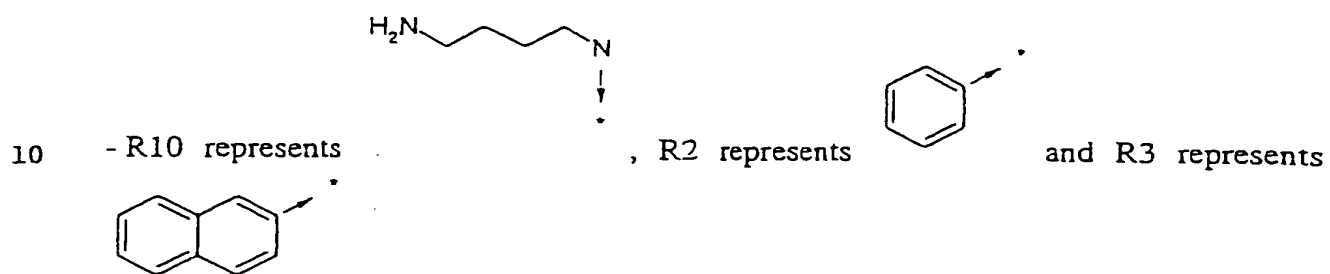
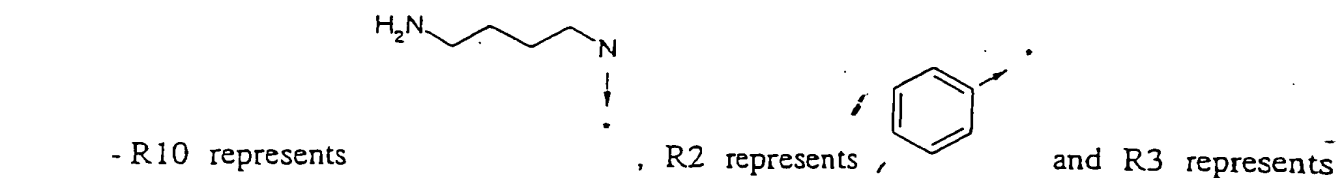


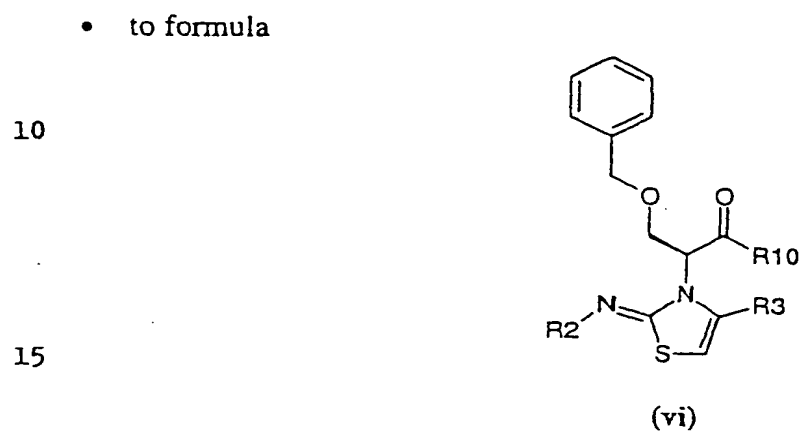
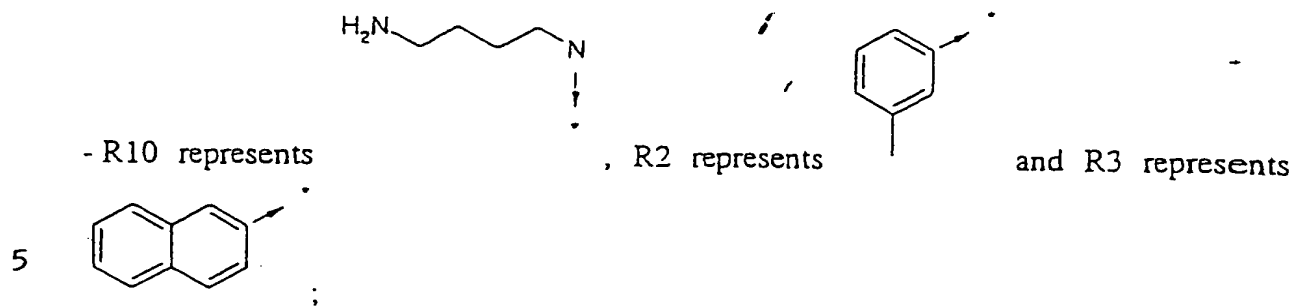
, R2 represents



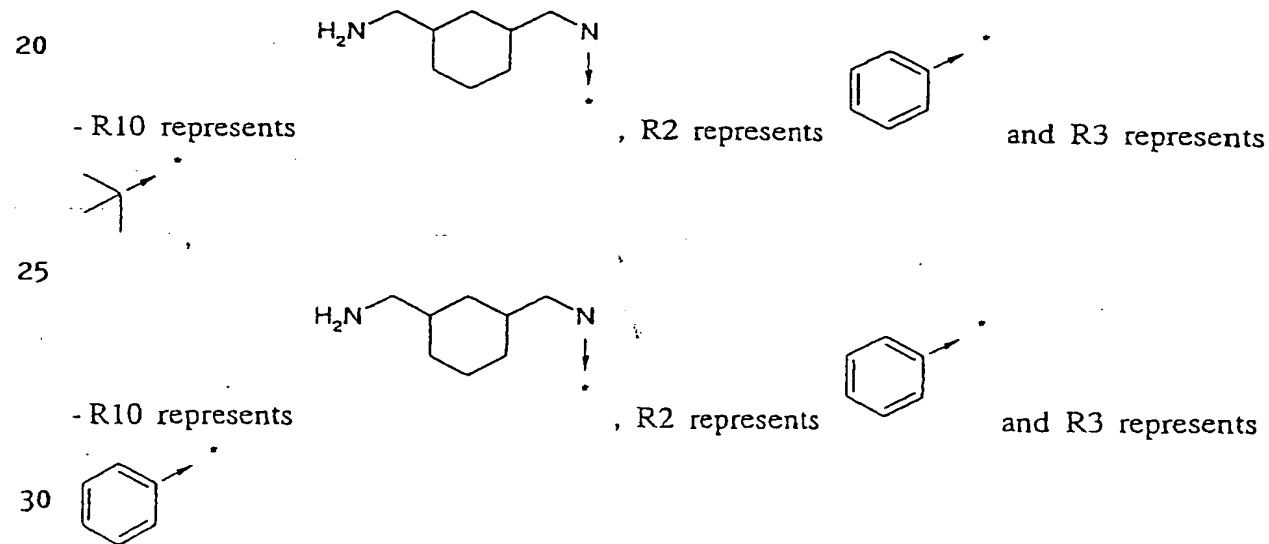
and R3 represents

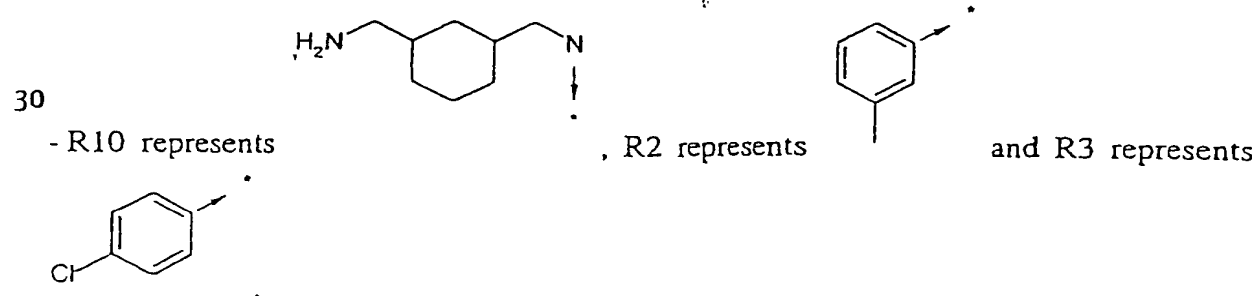
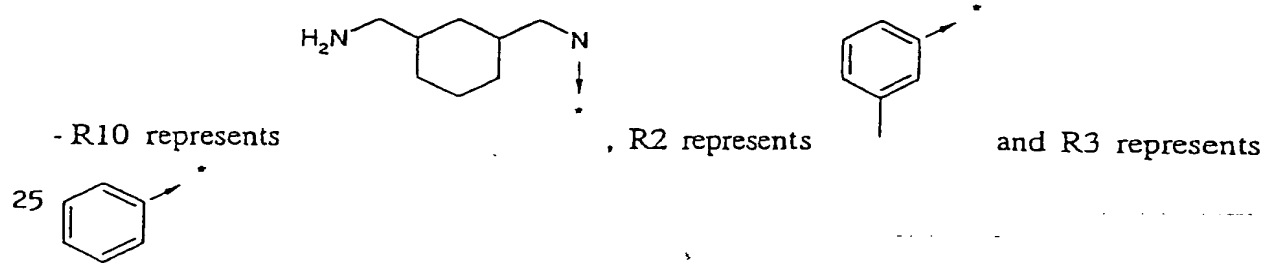
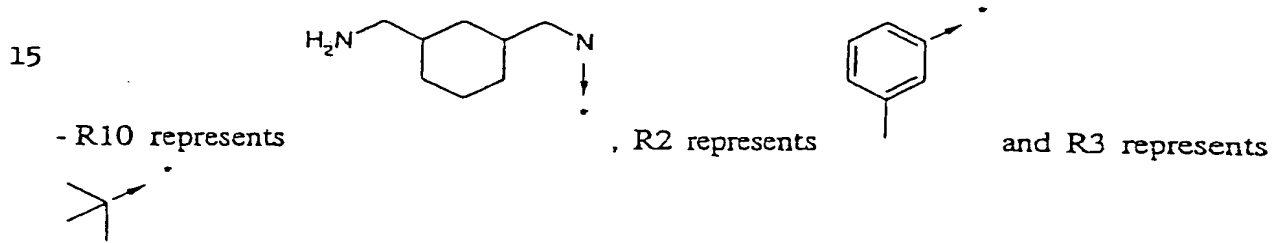
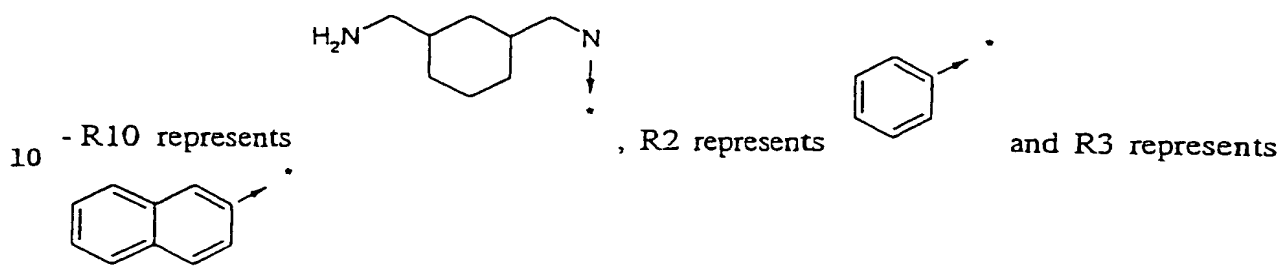
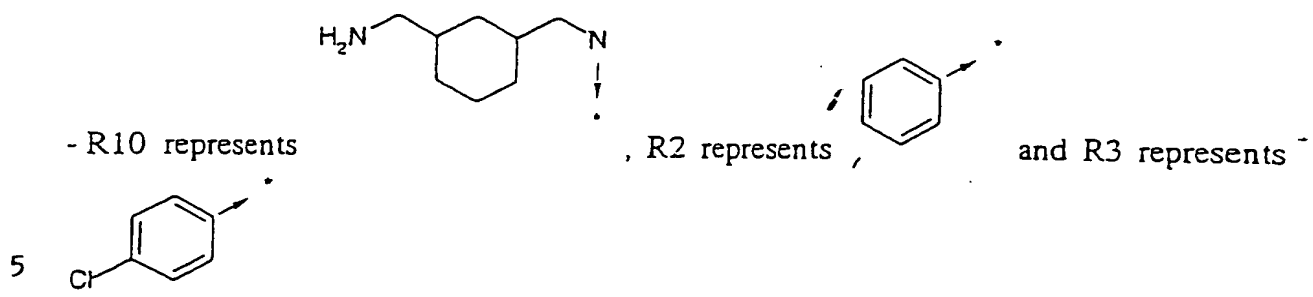
35

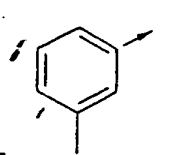
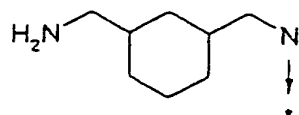




in which:



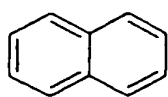




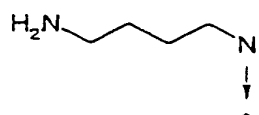
- R10 represents

, R2 represents

and R3 represents

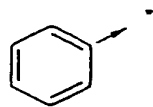


5



- R10 represents

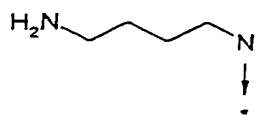
, R2 represents



and R3 represents

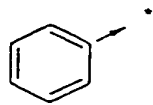


10



- R10 represents

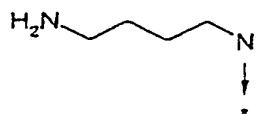
, R2 represents



and R3 represents

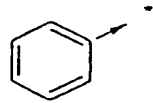


15

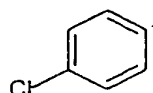


- R10 represents

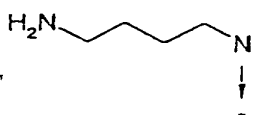
, R2 represents



and R3 represents

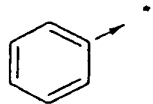


25

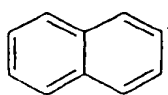


- R10 represents

, R2 represents



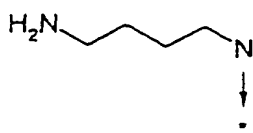
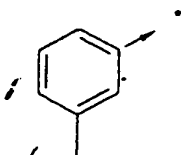
and R3 represents

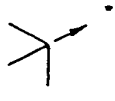


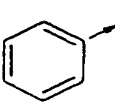
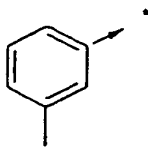
30

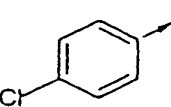
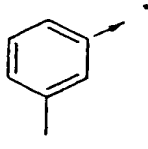
35



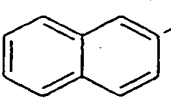
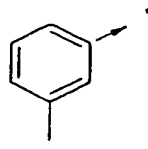
- R10 represents , R2 represents  and R3 represents



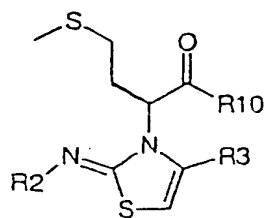
- R10 represents , R2 represents  and R3 represents

- R10 represents , R2 represents  and R3 represents

, or finally

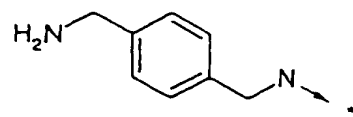
- R10 represents , R2 represents  and R3 represents

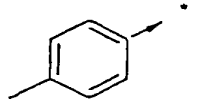
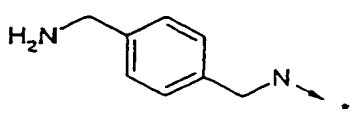
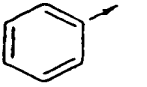
to formula

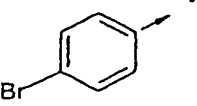
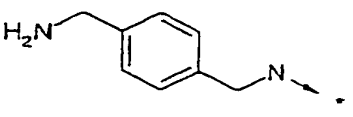
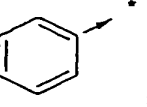


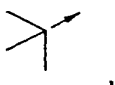
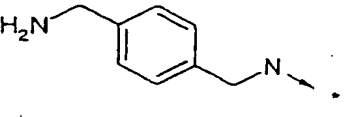
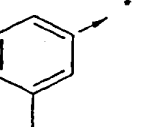
(vii)

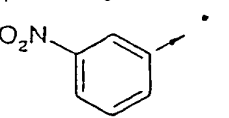
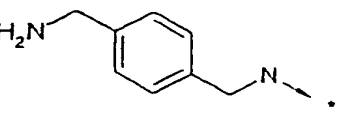
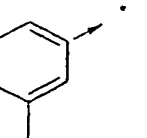
in which:

5 - R10 represents  , R2 represents  and R3 represents 

10 - R10 represents  , R2 represents  and R3 represents 

15 - R10 represents  , R2 represents  and R3 represents 

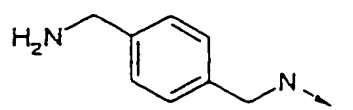
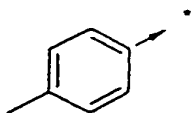
20 - R10 represents  , R2 represents  and R3 represents 

25 - R10 represents  , R2 represents  and R3 represents 

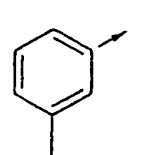
30

35

- R10 represents



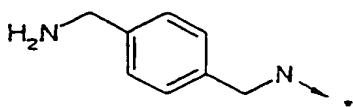
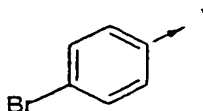
, R2 represents



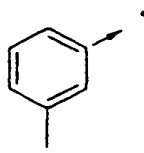
and R3 represents

5

- R10 represents



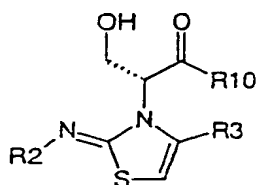
, R2 represents



and R3 represents

10

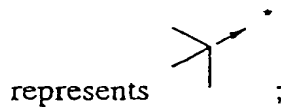
15 • to formula



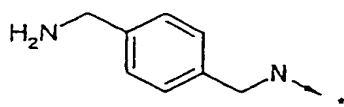
(viii)

20

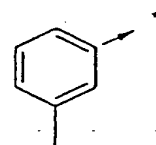
in which R10 represents



represents



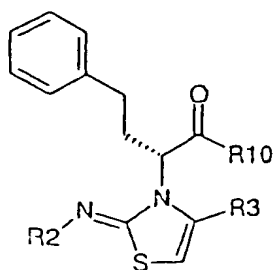
, R2 represents



and R3

25

• to formula

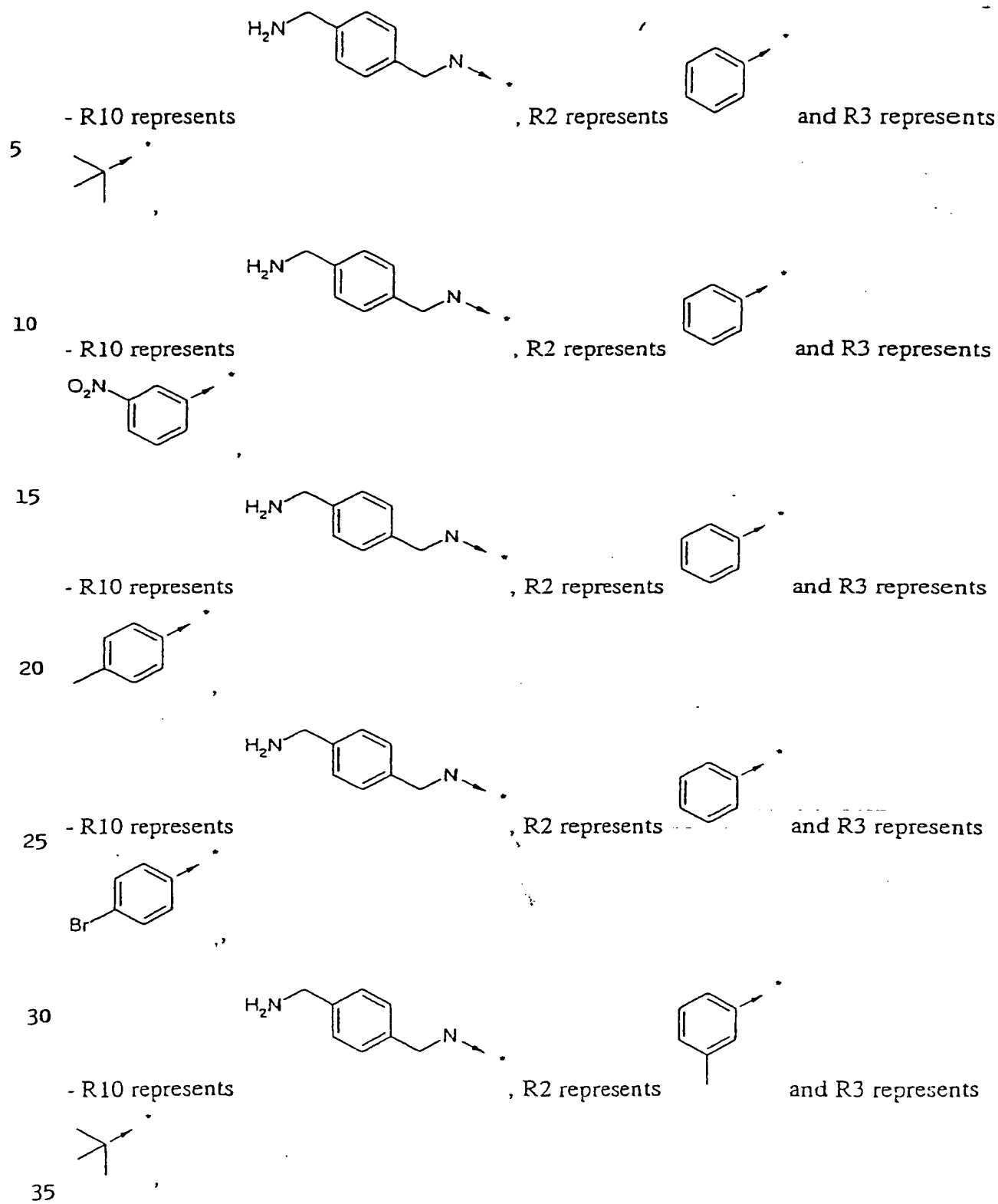


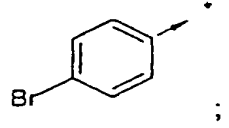
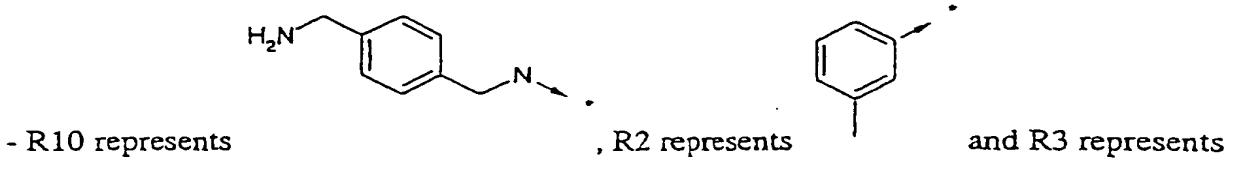
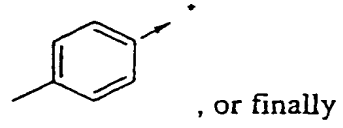
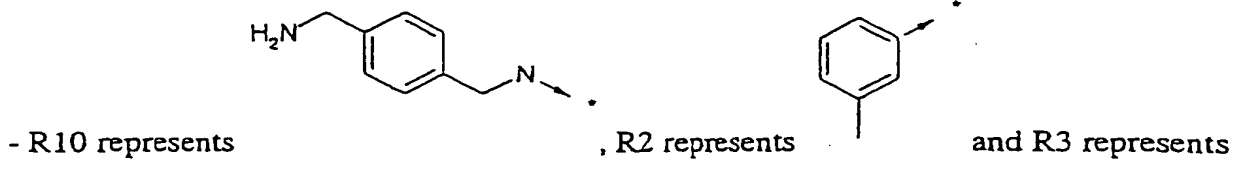
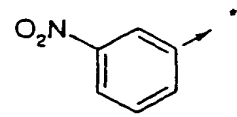
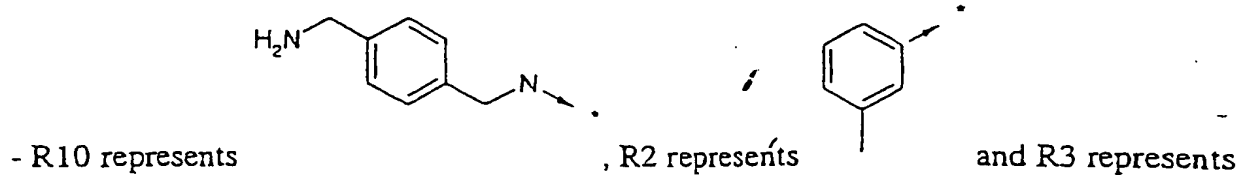
(ix)

30

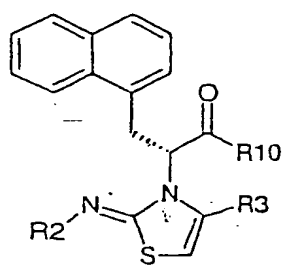
35

in which:



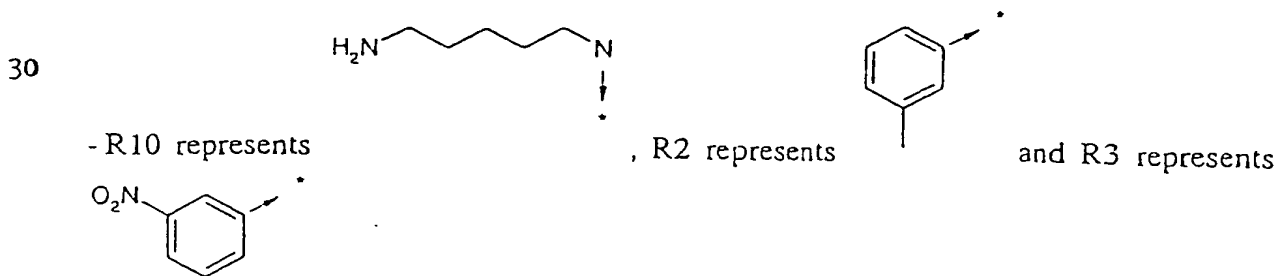
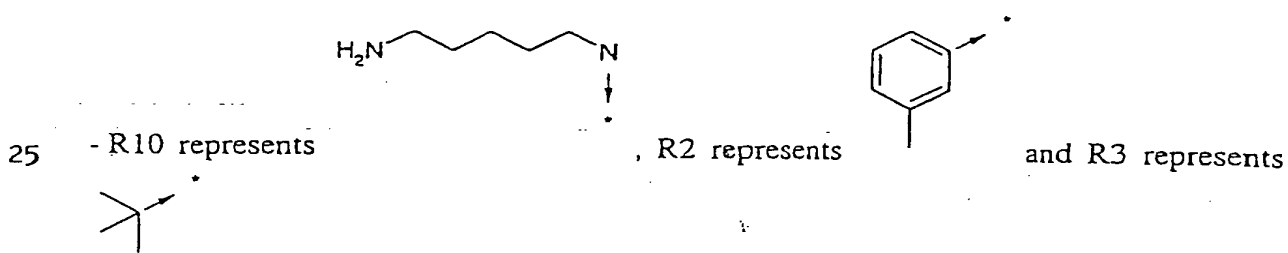
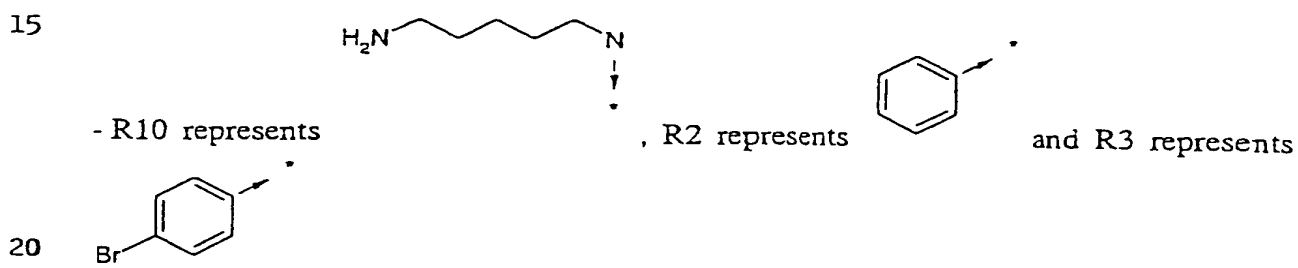
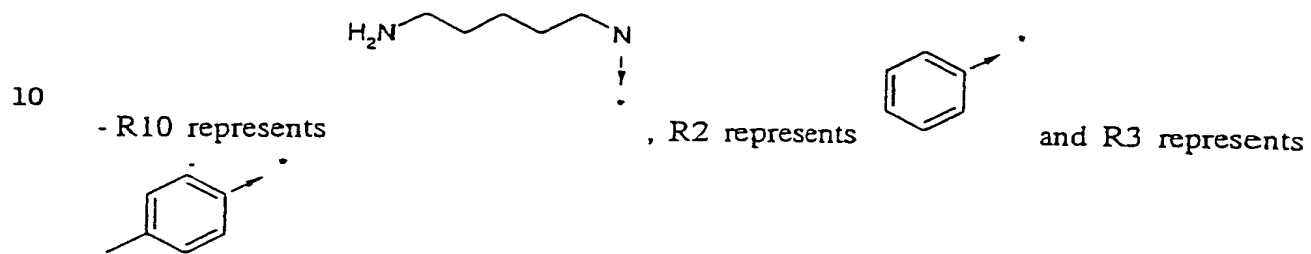
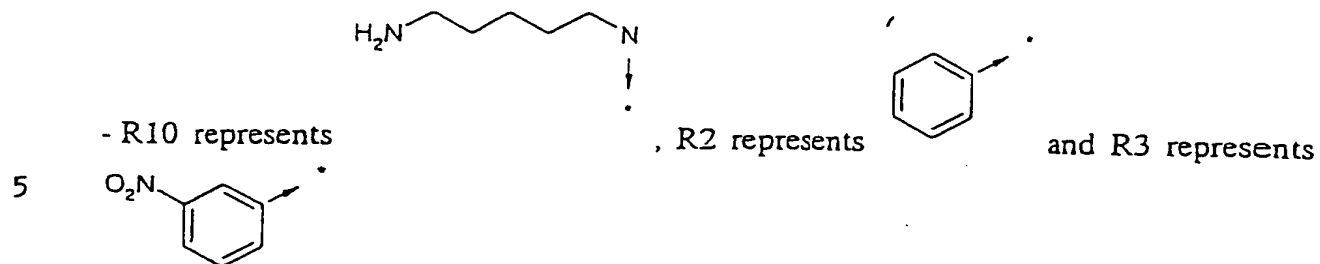


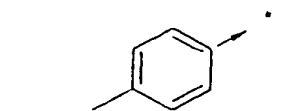
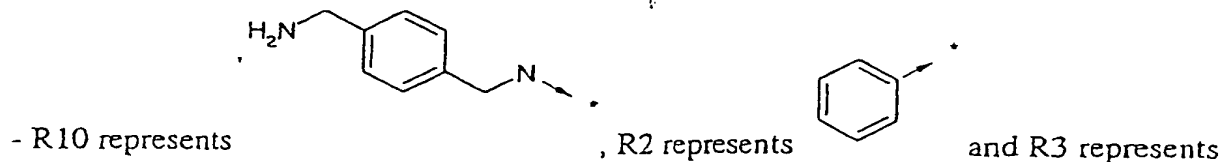
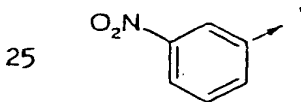
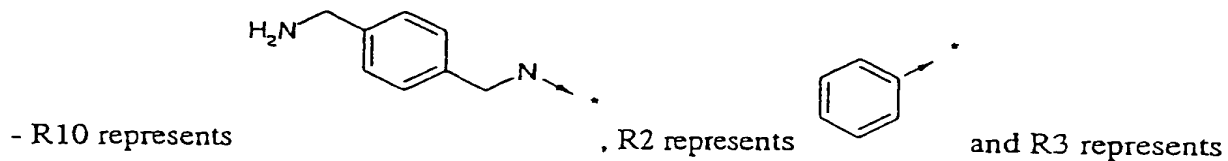
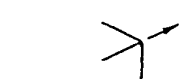
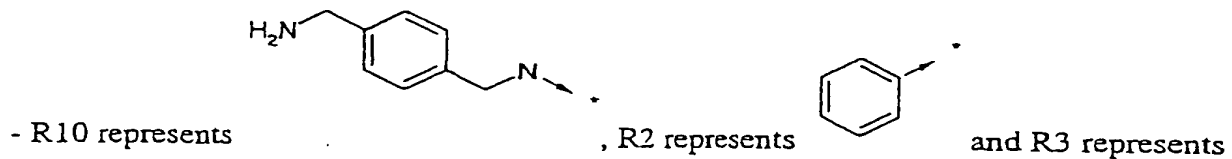
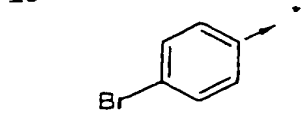
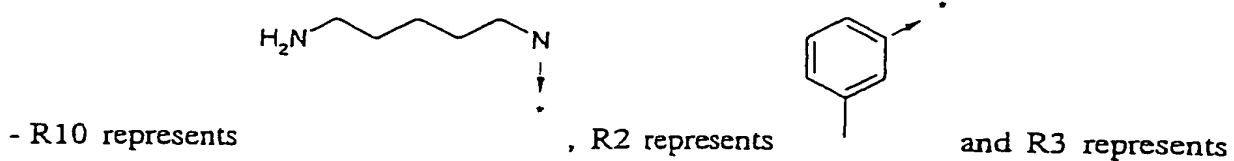
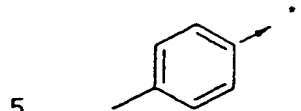
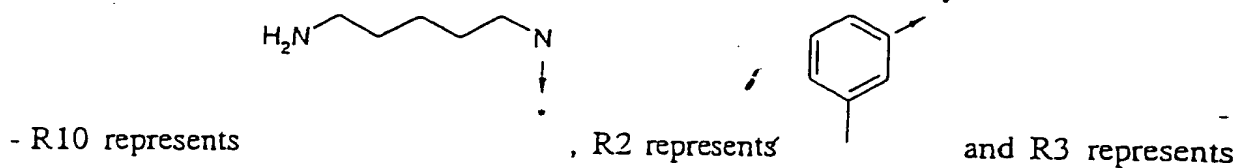
• to formula

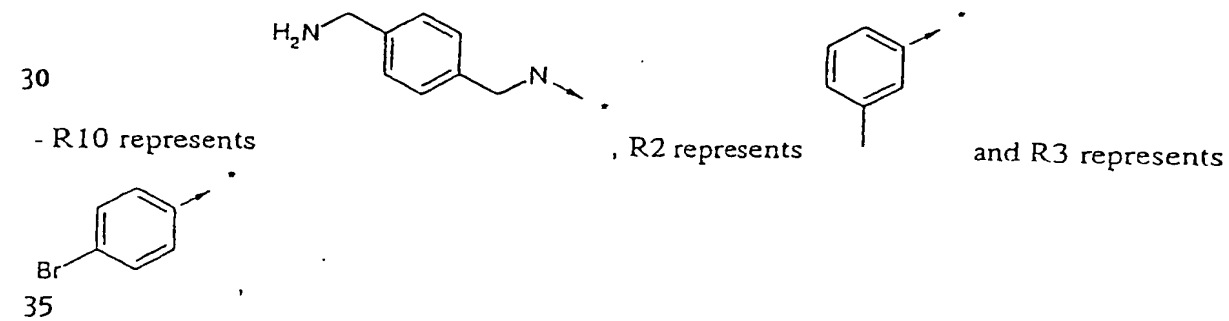
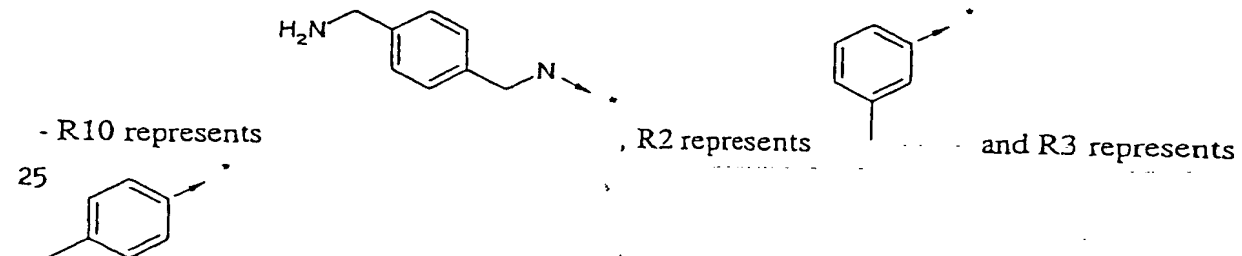
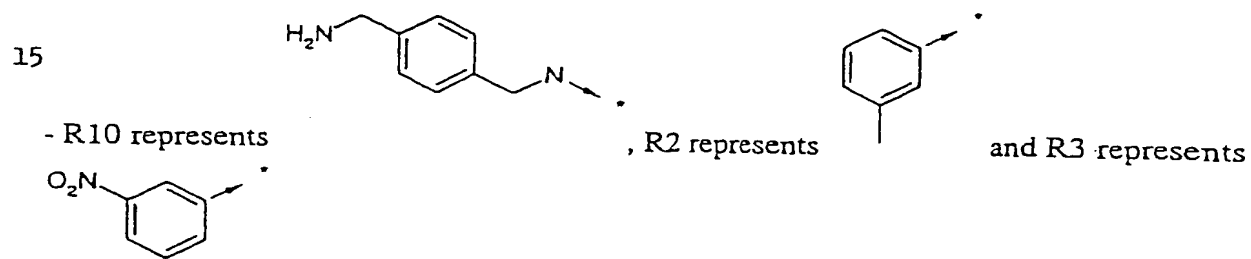
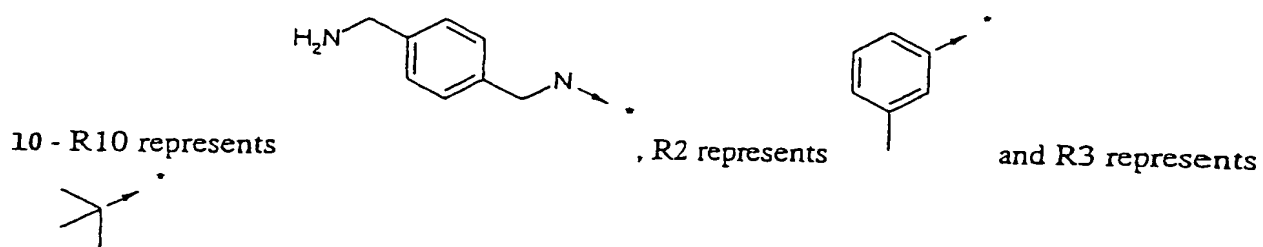
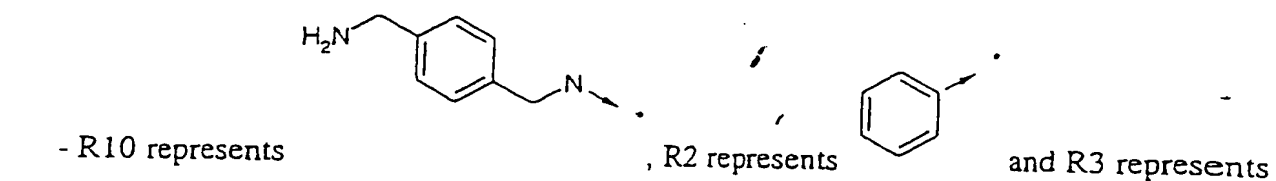


(x)

in which:

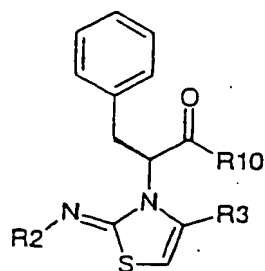






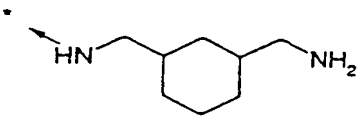
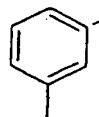


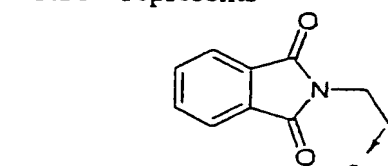
• to formula



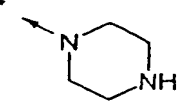
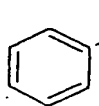
(xi)

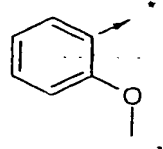
in which:

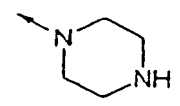
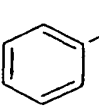
- R10 represents , R2 represents  and R3

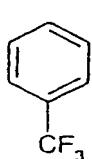


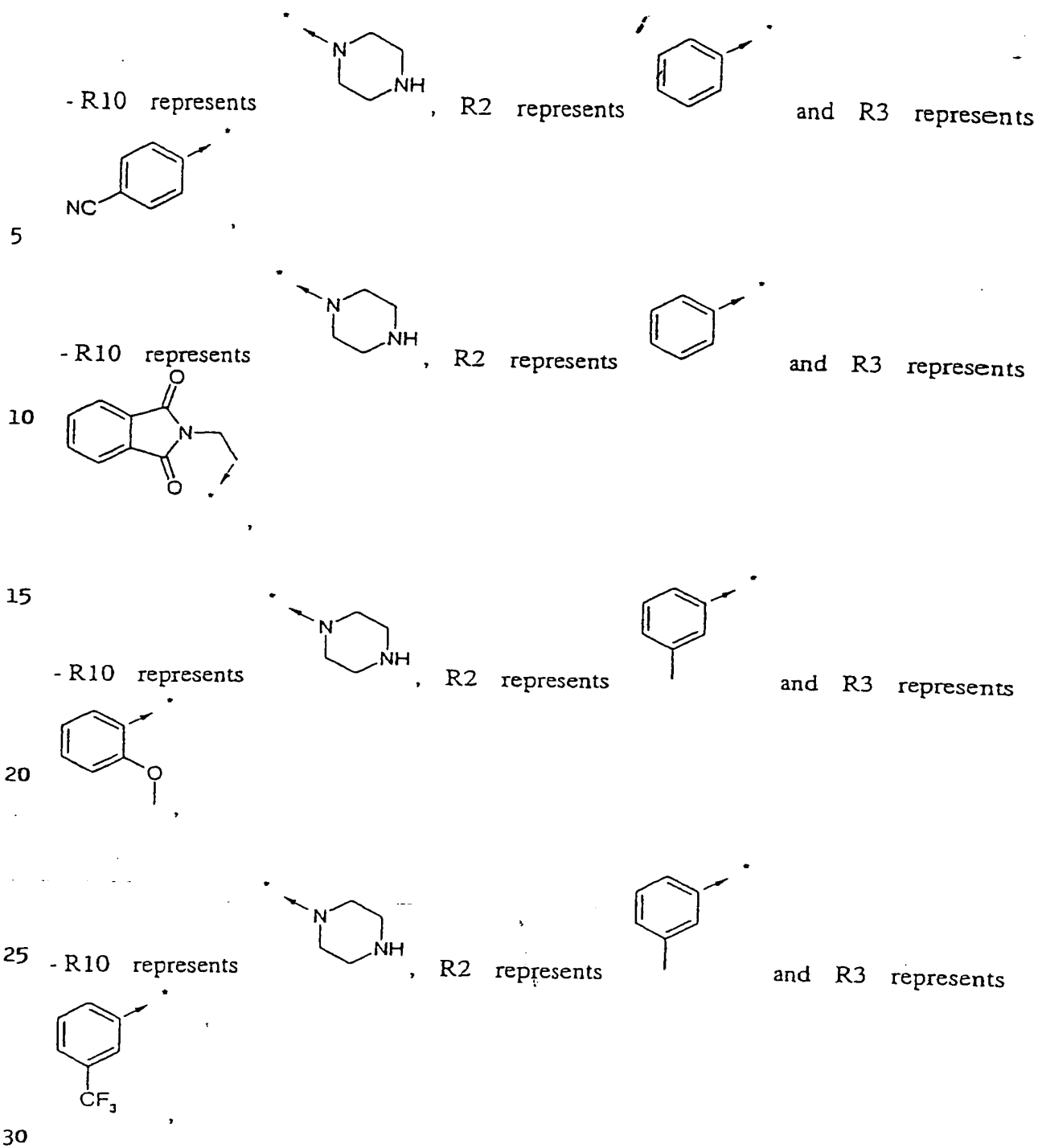
represents

- R10 represents , R2 represents  and R3 represents

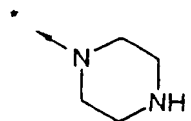


- R10 represents , R2 represents  and R3 represents

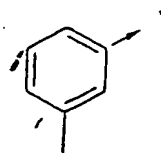




- R10 represents

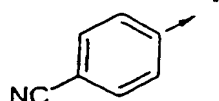


, R2 represents



and R3 represents

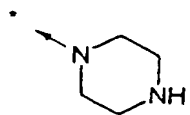
5



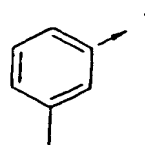
, or finally

10

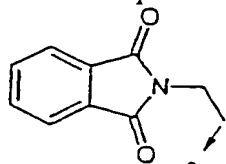
- R10 represents



, R2 represents

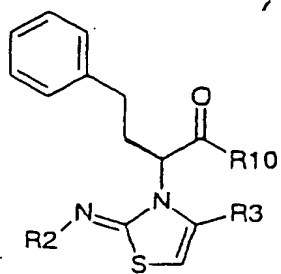


and R3 represents



• to formula

5

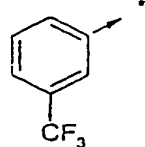


(xii)

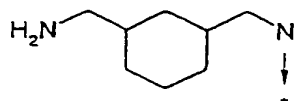
in which:

10

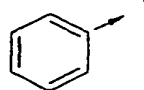
- R10 represents



15



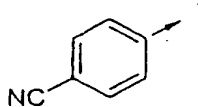
, R2 represents



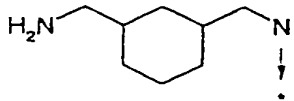
and R3 represents

20

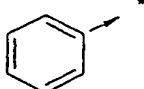
- R10 represents



25



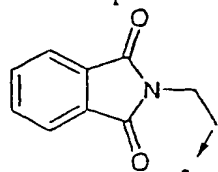
, R2 represents



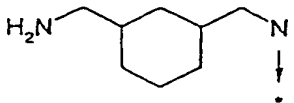
and R3 represents

30

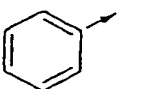
- R10 represents



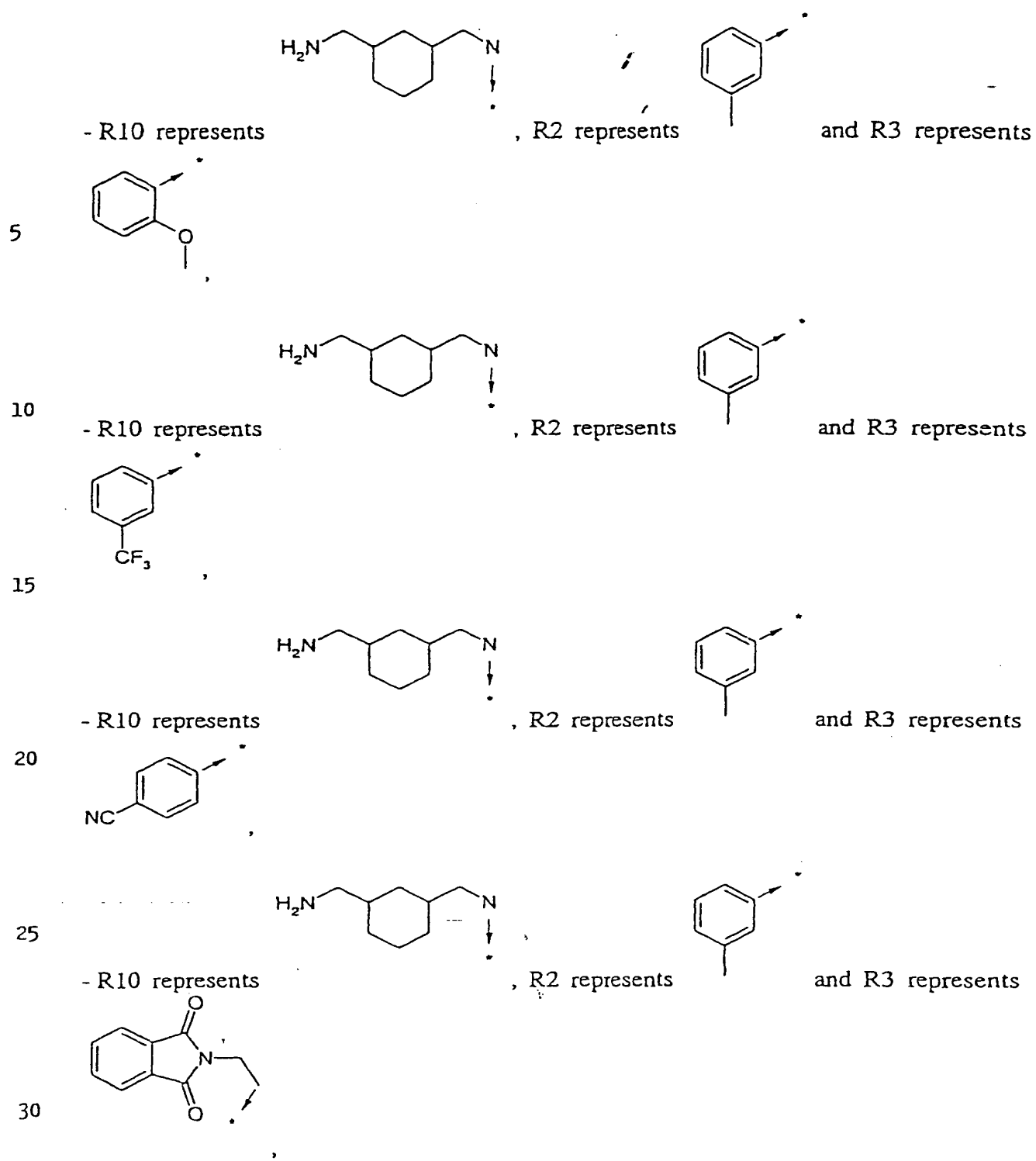
35



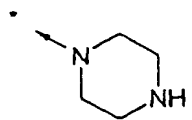
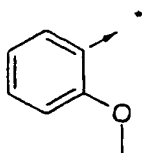
, R2 represents



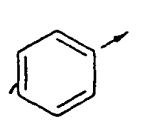
and R3 represents



- R10 represents



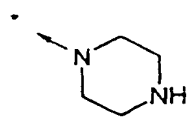
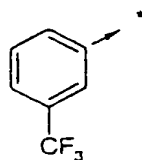
, R2 represents



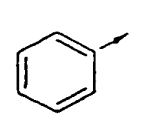
and R3 represents

5

- R10 represents



, R2 represents

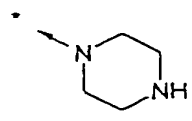
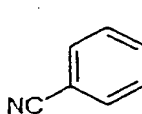


and R3 represents

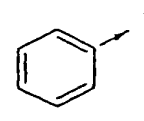
10

15

- R10 represents



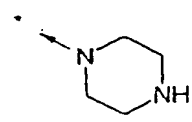
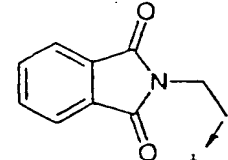
, R2 represents



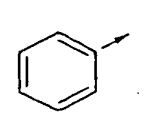
and R3 represents

20

- R10 represents



, R2 represents

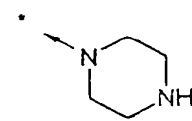
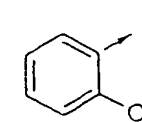


and R3 represents

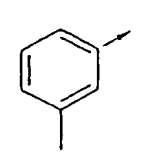
25

30

- R10 represents

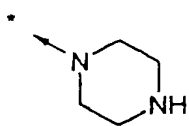


, R2 represents

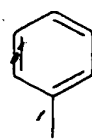


and R3 represents

- R10 represents

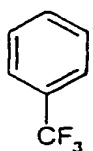


, R2 represents



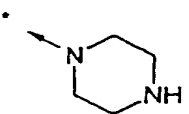
and R3 represents

5

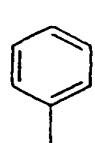


10

- R10 represents

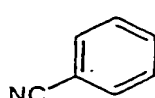


, R2 represents



and R3 represents

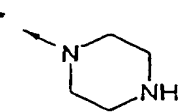
NC



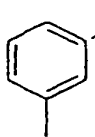
, or finally

15

- R10 represents

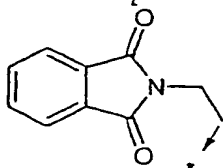


, R2 represents



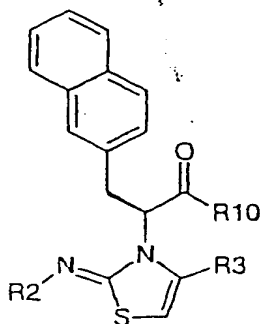
and R3 represents

20



• to formula

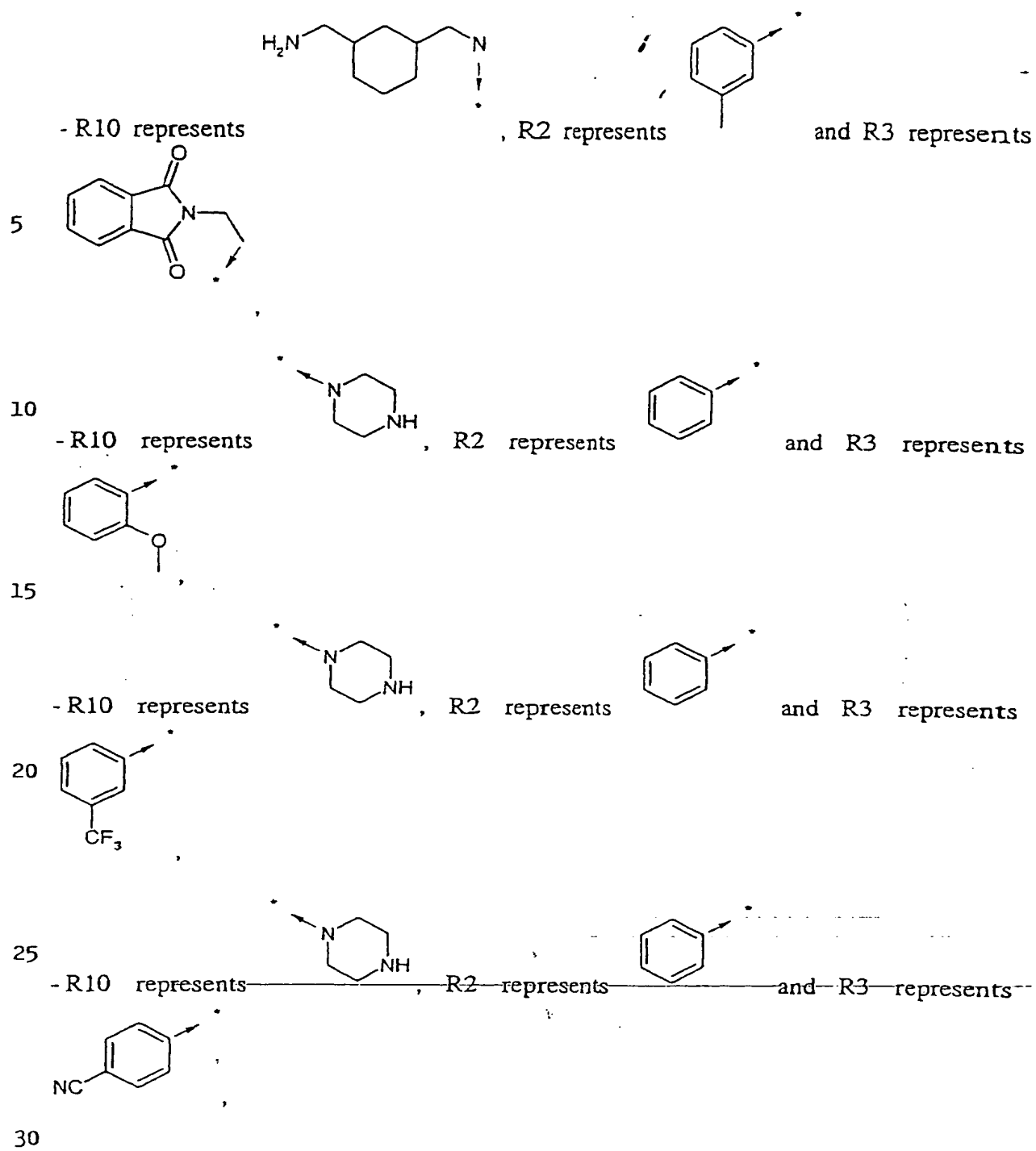
25



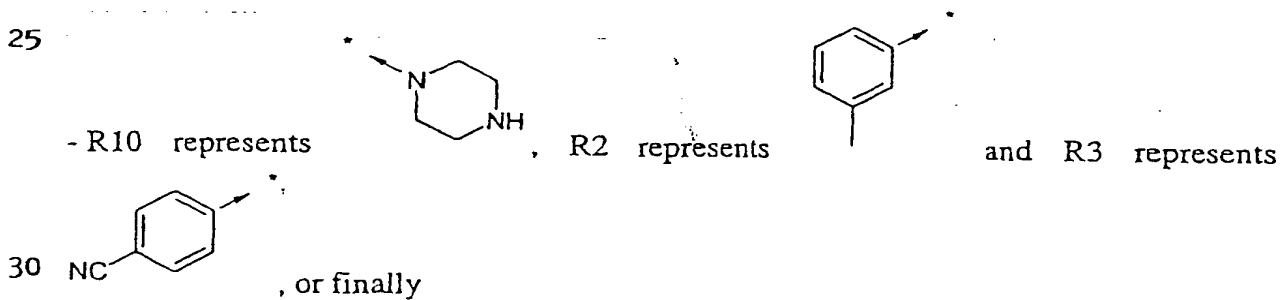
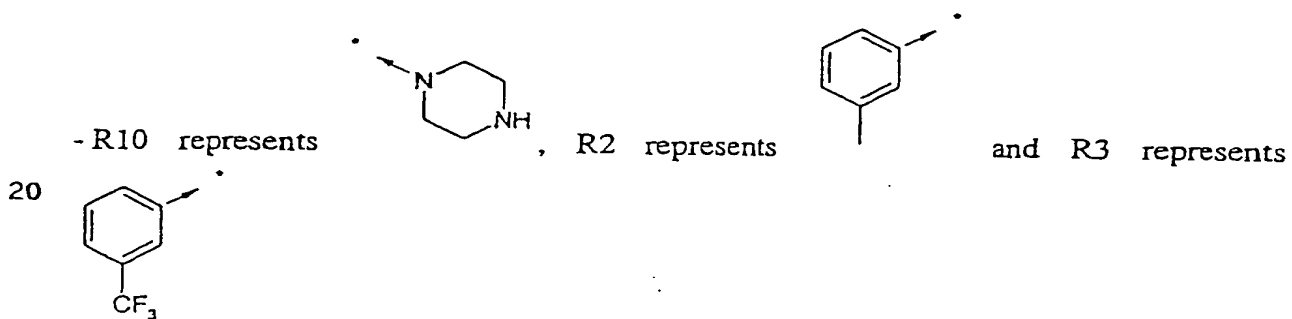
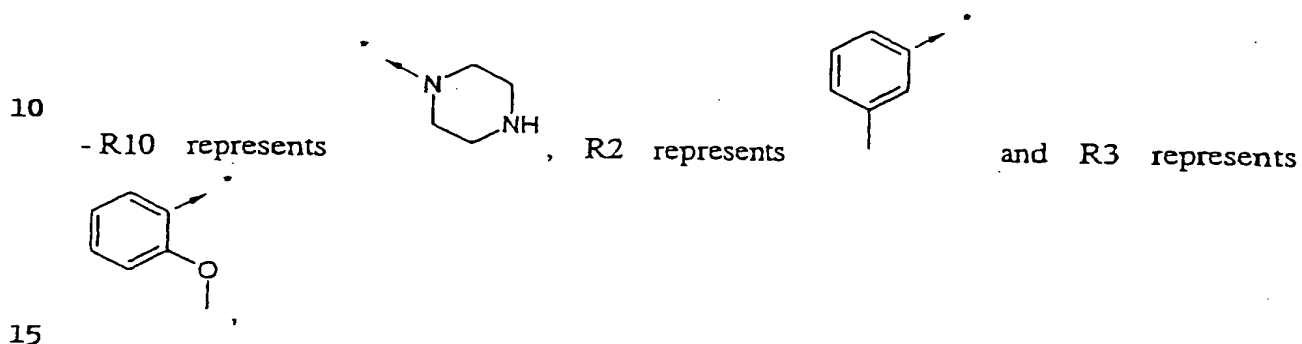
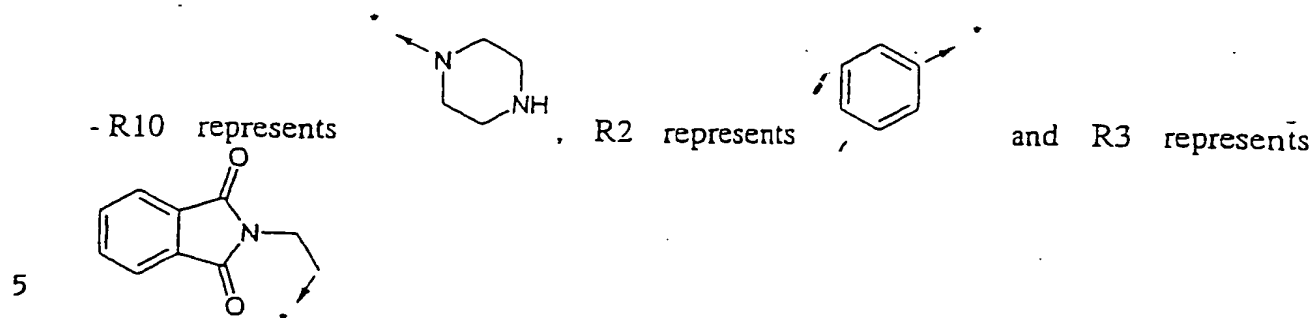
(xiii)

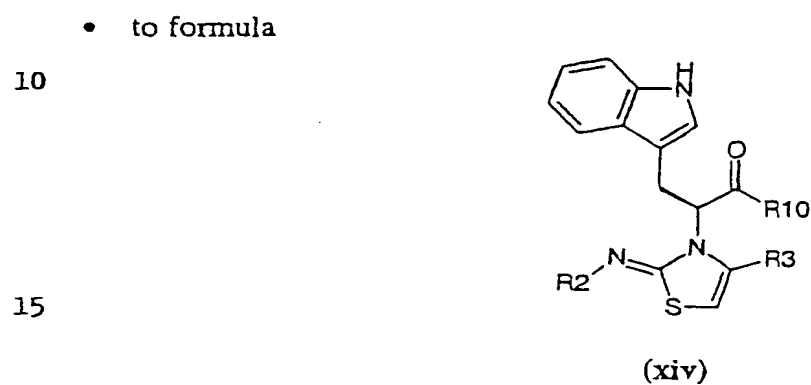
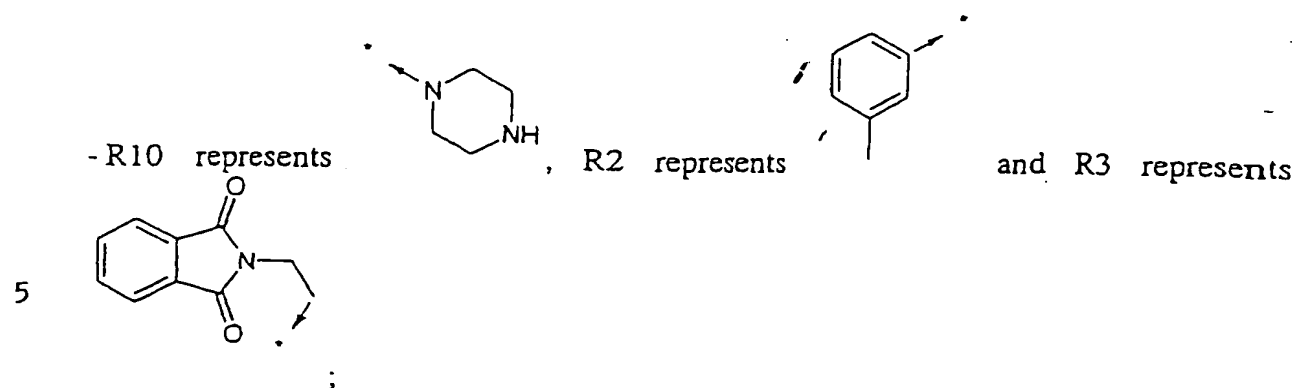
30

35 in which:

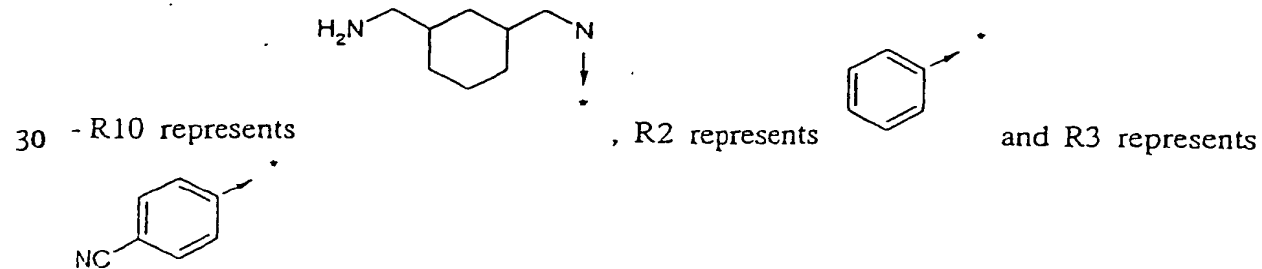
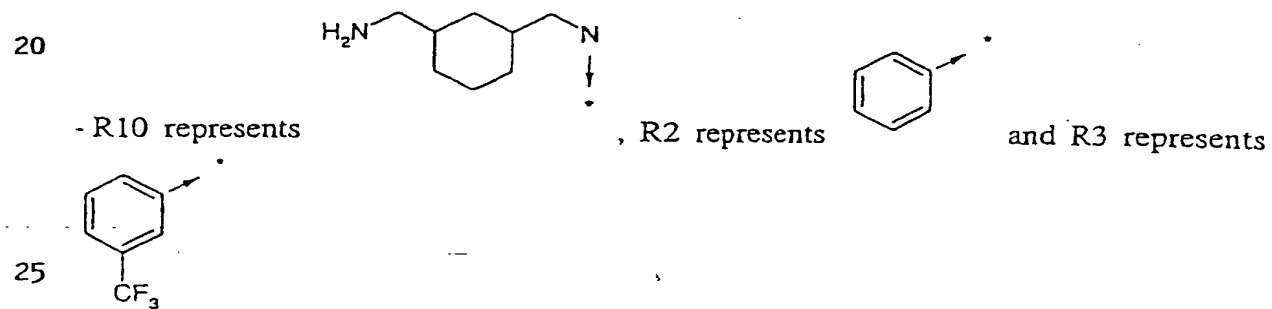


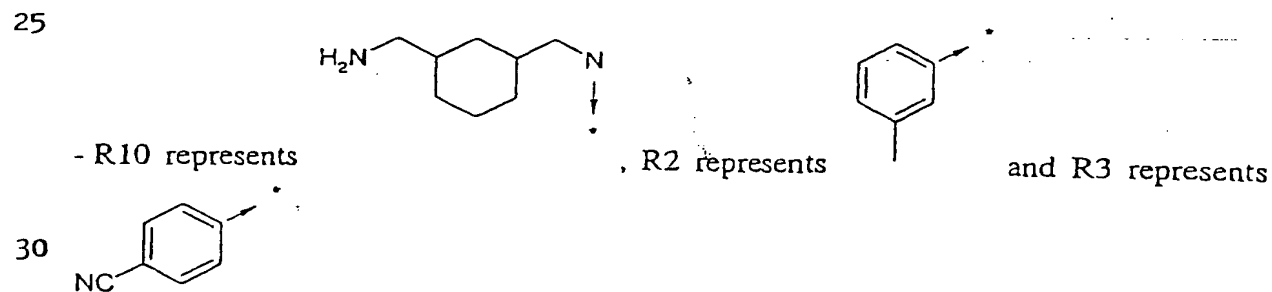
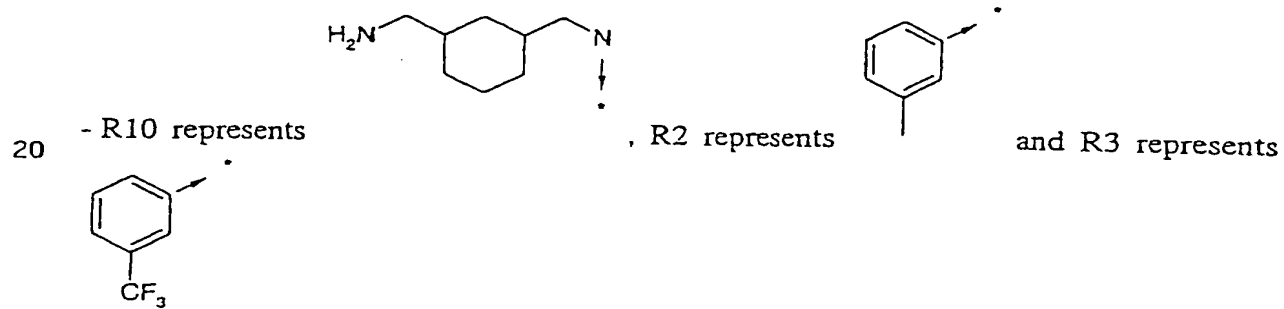
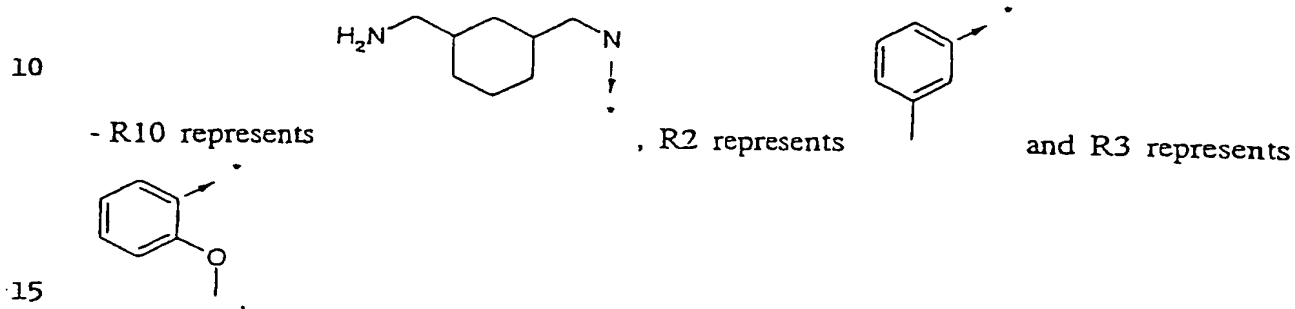
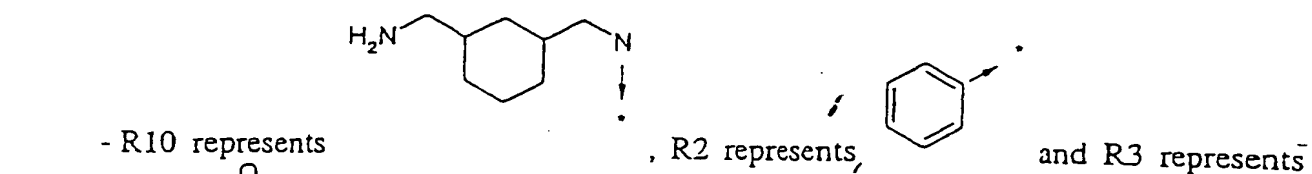


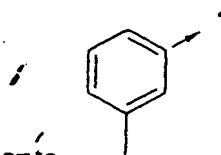
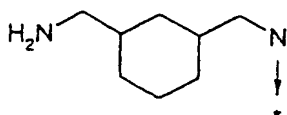




in which:





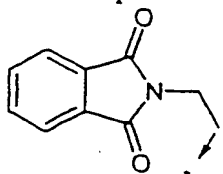


- R10 represents

, R2 represents

and R3 represents

5

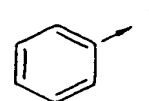
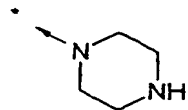
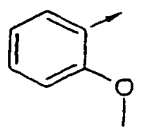


10

- R10 represents

, R2 represents

and R3 represents



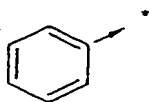
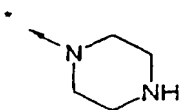
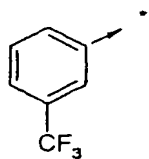
15

- R10 represents

, R2 represents

and R3 represents

20

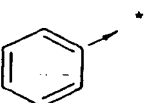
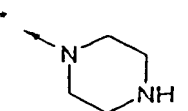
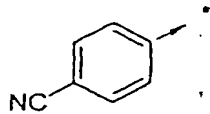


25

- R10 represents

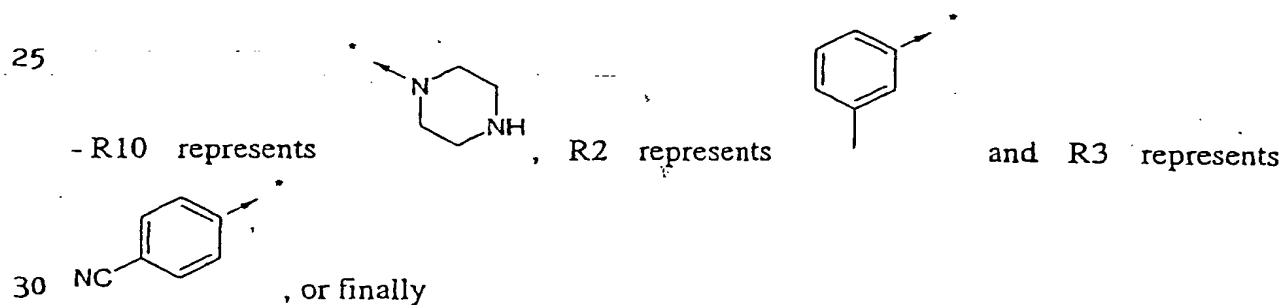
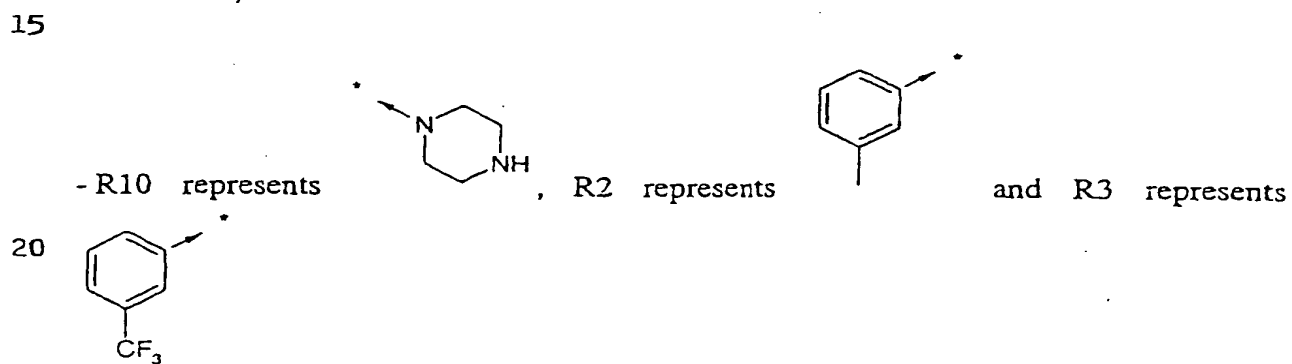
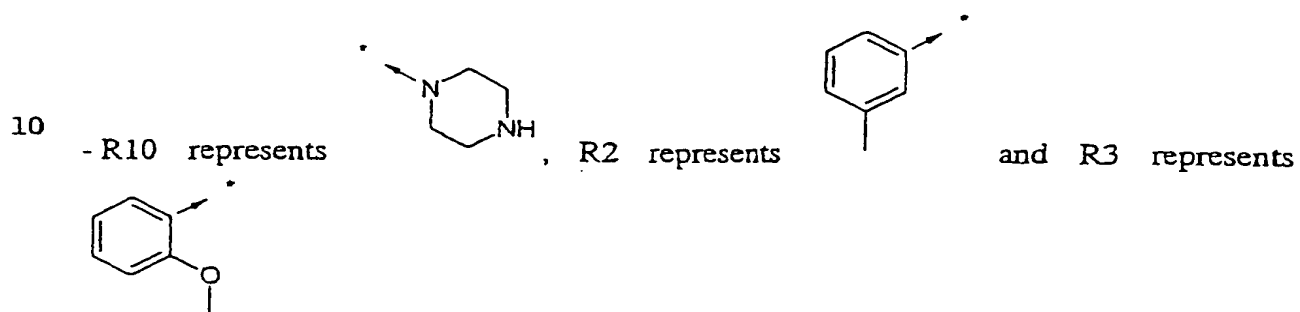
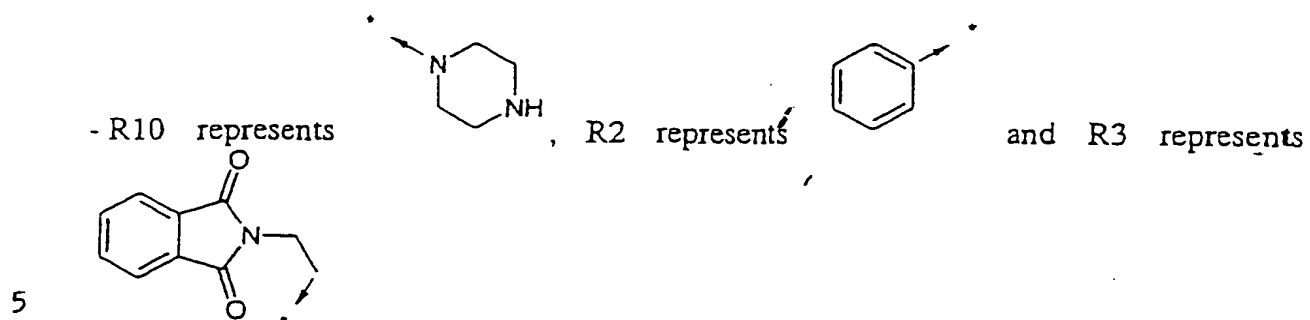
, R2 represents

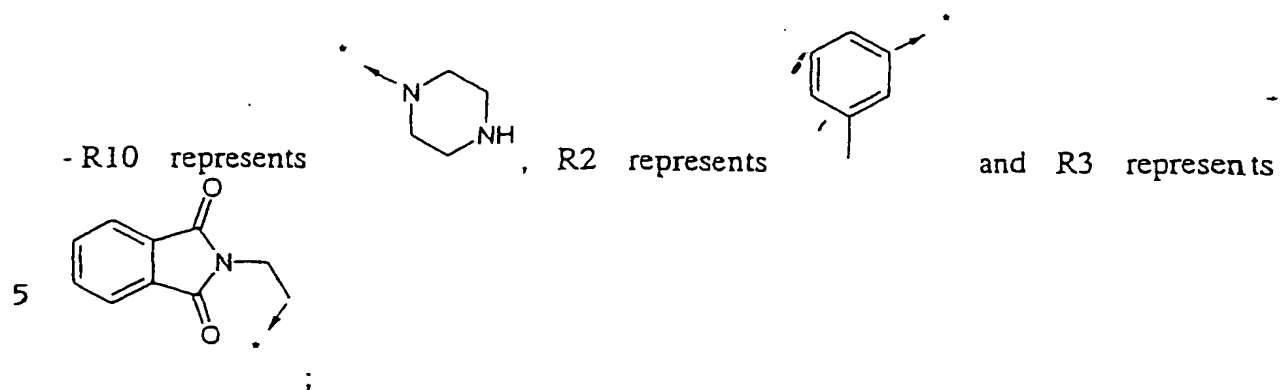
and R3 represents



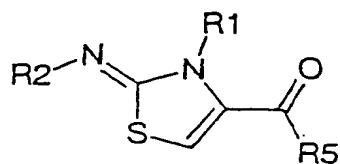
30

35



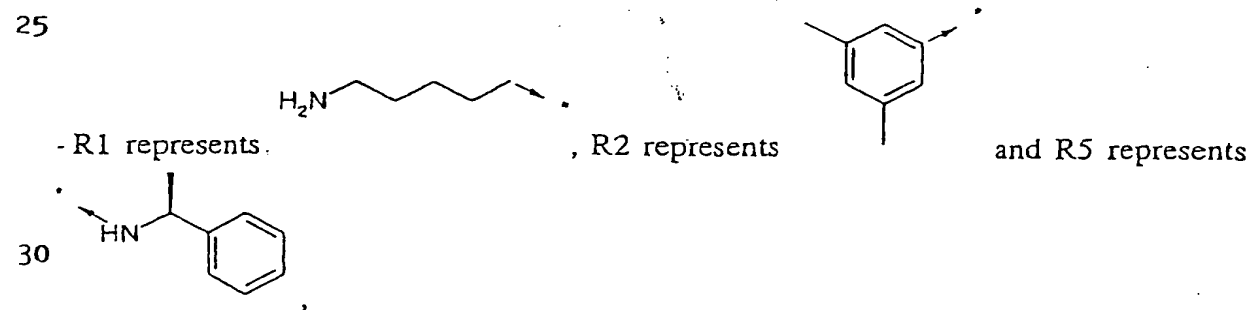
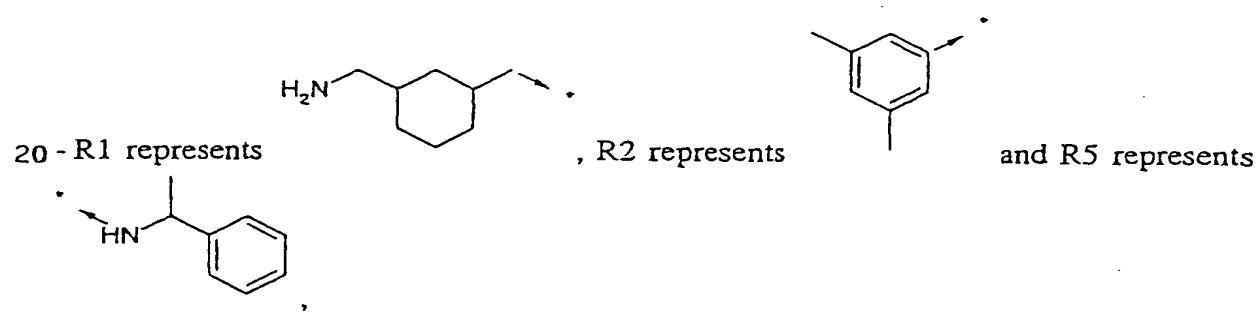


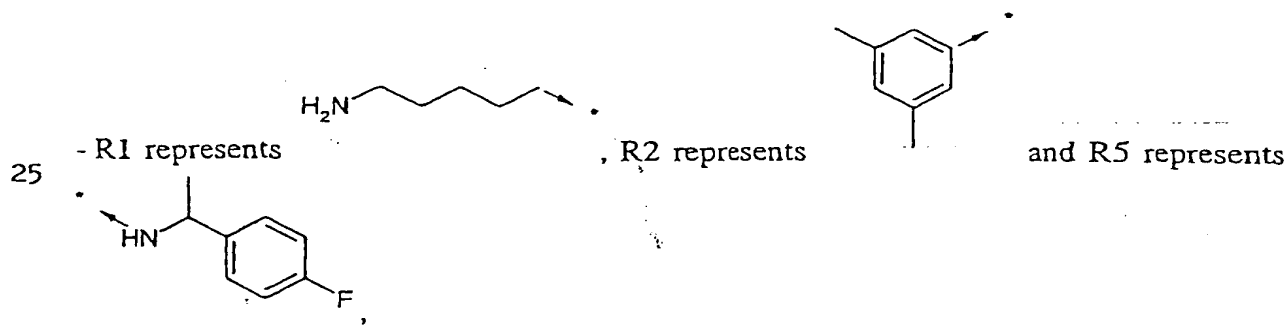
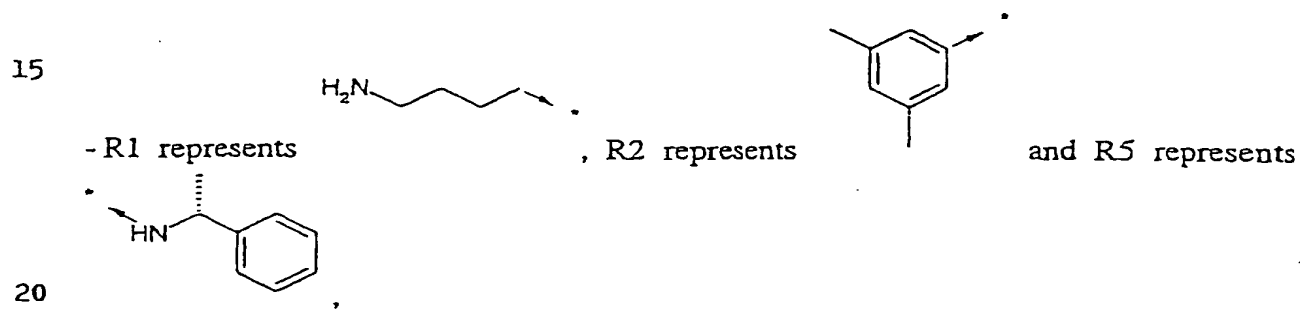
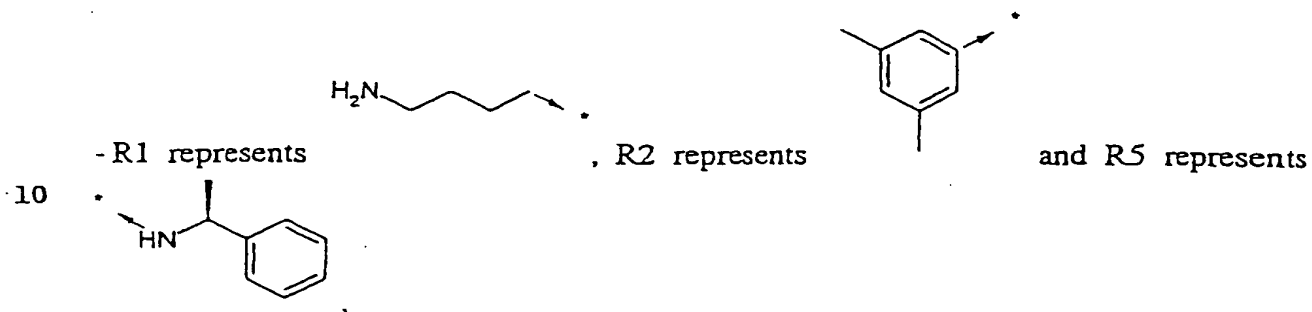
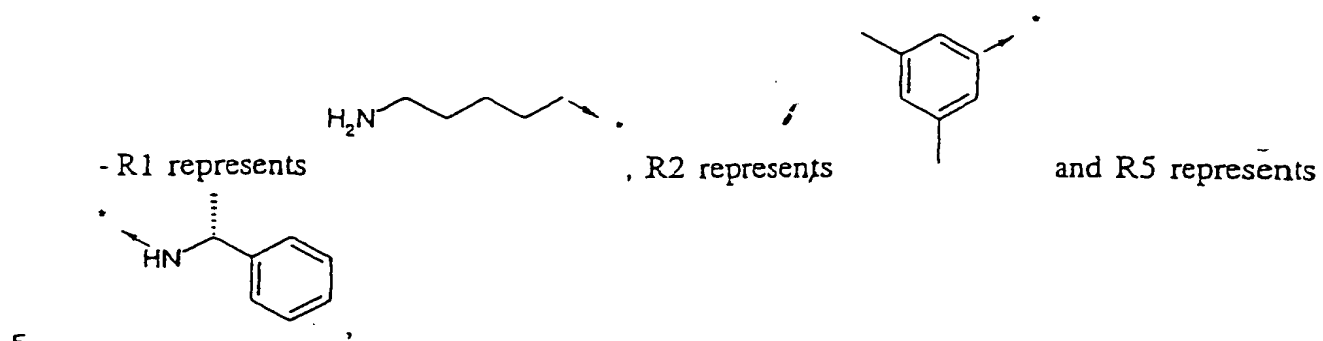
10 or finally to formula



(xv)

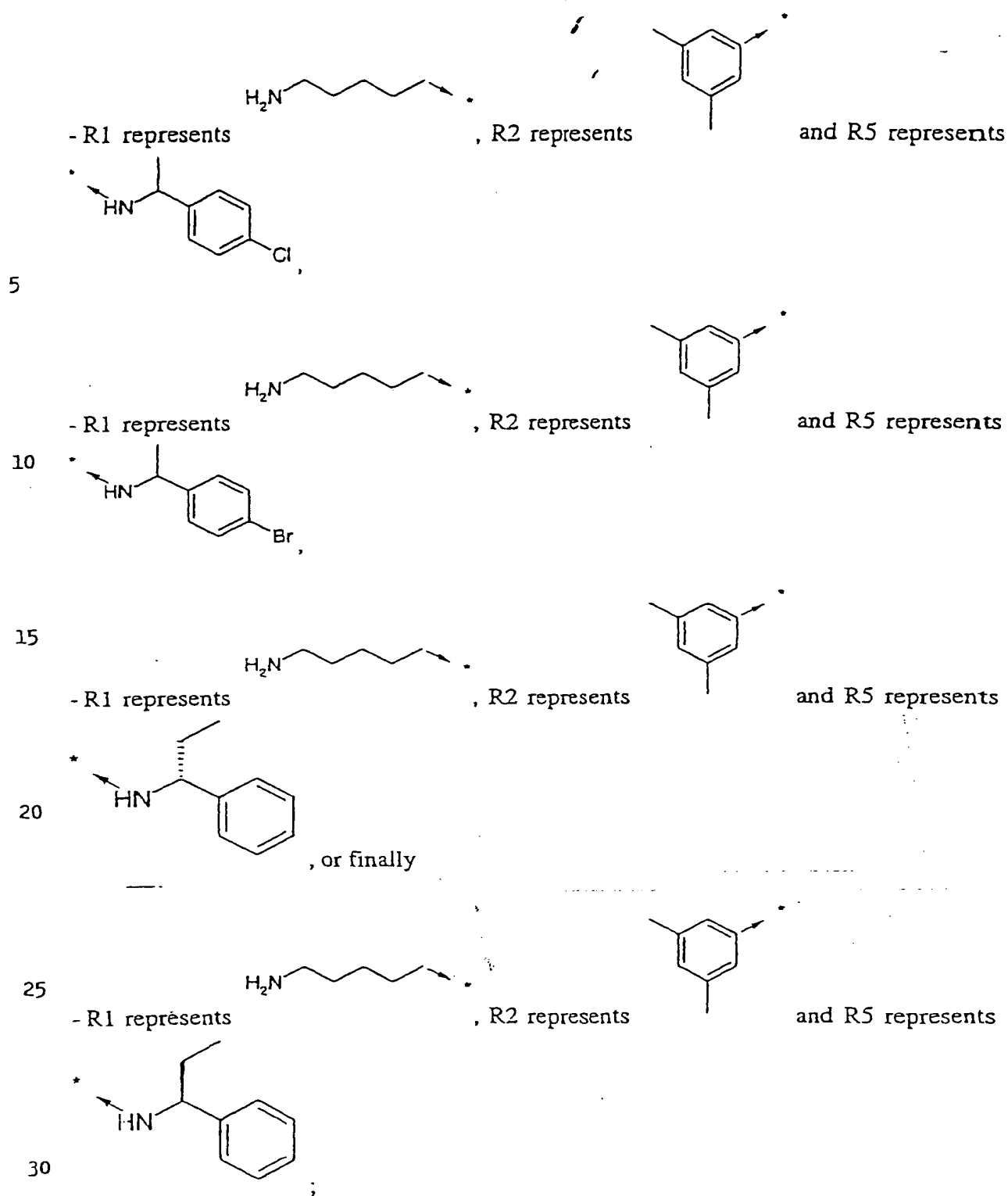
15 in which:





30

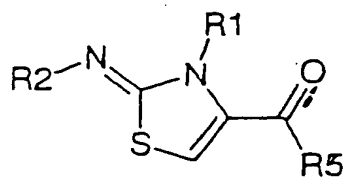
35



or a salt of one of these compounds.

2. Compound according to claim 1, characterized in that it corresponds to the formula





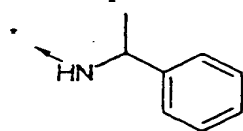
(xv)

5

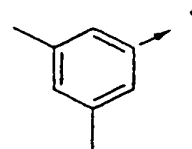
in which:

10

- R1 represents



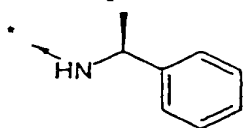
, R2 represents



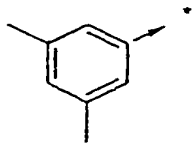
and R5 represents

15

- R1 represents



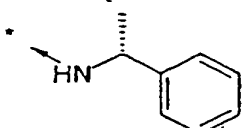
, R2 represents



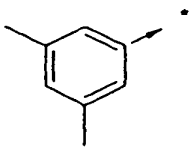
and R5 represents

20

- R1 represents



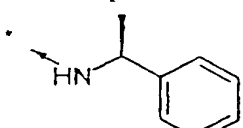
, R2 represents



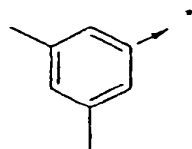
and R5 represents

25

- R1 represents



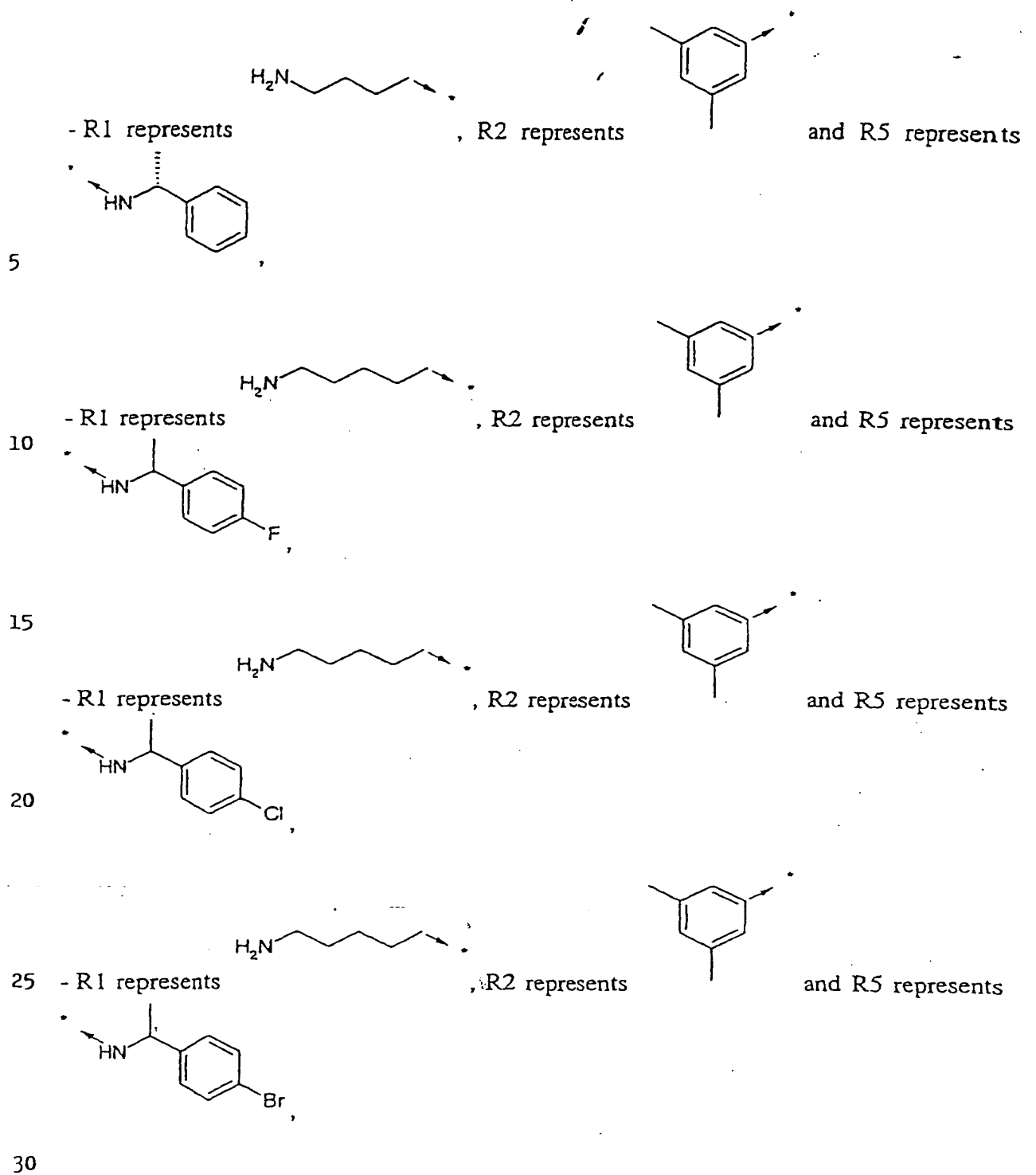
, R2 represents

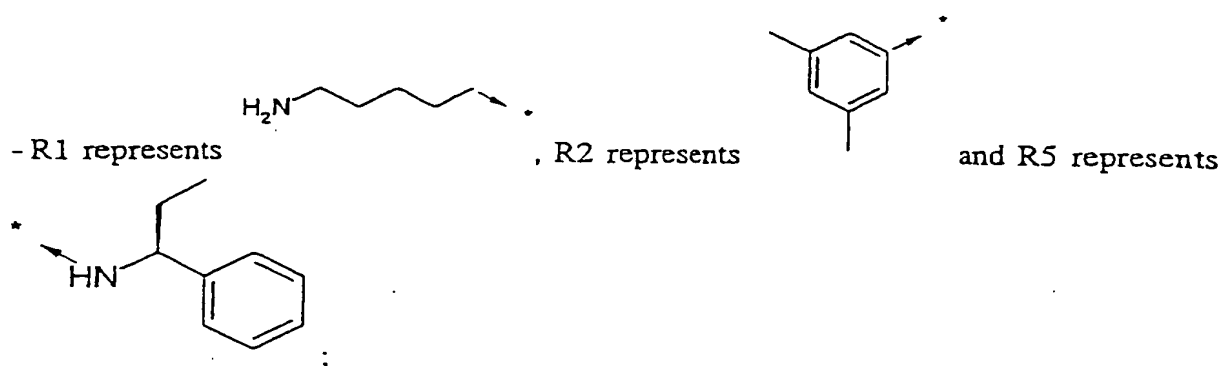
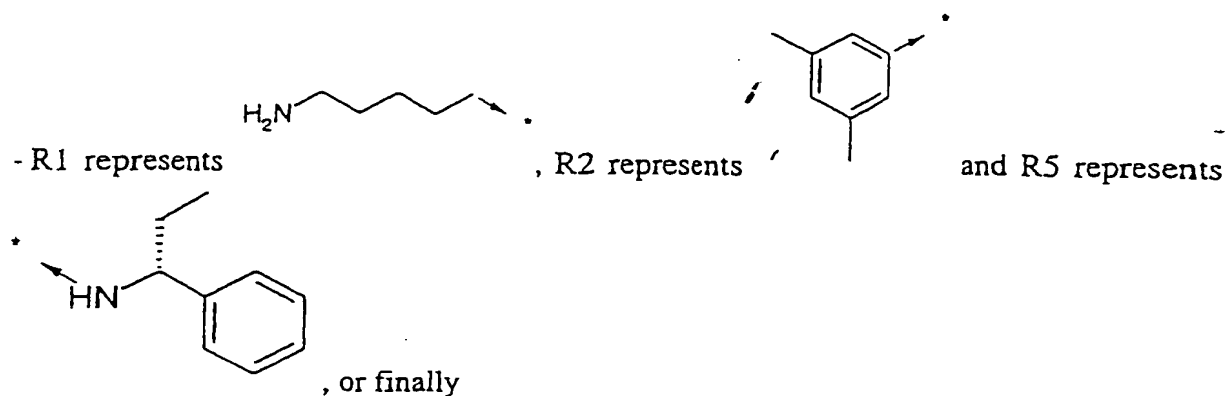


and R5 represents

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5 or a salt of one of these compounds.

3. As a medicament, a compound according to claim 1 or 2 or a pharmaceutically acceptable salt of said compound.

4. Pharmaceutical composition comprising, as active ingredient, a compound according to claim 1 or 2 or a pharmaceutically acceptable salt of said compound.

10 5. Use of a compound according to claim 1 or 2 or of a pharmaceutically acceptable salt of said compound for preparing a medicament intended to treat the pathological states or diseases in which one (or several) of the somatostatin receptors is (are) involved.

15 6. Use according to claim 5, characterized in that the pathological states or the diseases to be treated are chosen from the group comprising the following pathological states or diseases: acromegalia, hypophyseal adenomas, Cushing's disease, gonadotrophinomas and prolactinomas, catabolic side-effects of glucocorticoids, insulin dependent diabetes, diabetic retinopathy, diabetic nephropathy, syndrome X, dawn phenomenon, angiopathy, angioplasty, hyperthyroidism, gigantism, endocrinic gastroenteropancreatic  
20 tumors including carcinoid syndrome, VIPoma, insulinoma, nesidioblastoma, hyperinsulinemia, glucagonoma, gastrinoma and Zollinger-Ellison's syndrome,

GRFoma as well as acute bleeding of the esophageal varices, ulcers, gastroesophageal reflux, gastroduodenal reflux, pancreatitis, enterocutaneous and pancreatic fistulae but also diarrheas, refractory diarrheas of acquired immunodeficiency syndrome, chronic secretory diarrhea, diarrhea associated with irritable bowel syndrome, diarrheas induced  
5 by chemotherapy, disorders linked with gastrin releasing peptide, secondary pathologies with intestinal grafts, portal hypertension as well as hemorrhages of the varices in patients with cirrhosis, gastro-intestinal hemorrhage, hemorrhage of the gastroduodenal ulcer, bleeding of grafted vessels, Crohn's disease, systemic scleroses, dumping syndrome, small intestine syndrome, hypotension, scleroderma and medullar thyroid  
10 carcinoma, illnesses linked with cell hyperproliferation such as cancers and more particularly breast cancer, prostate cancer, thyroid cancer as well as pancreatic cancer and colorectal cancer, fibroses and more particularly fibrosis of the kidney, fibrosis of the liver, fibrosis of the lung, fibrosis of the skin, also fibrosis of the central nervous system as well as that of the nose and fibrosis induced by chemotherapy, and in other  
15 therapeutic fields, cephalaeas including cephalaea associated with hypophyseal tumors, pain, inflammatory disorders such as arthritis, panic attacks, chemotherapy, cicatrization of wounds, renal insufficiency resulting from delayed development, hyperlipidemia, obesity and delayed development linked with obesity, delayed uterine development, dysplasia of the skeleton, Noonan's syndrome, sleep apnea syndrome,  
20 Graves' disease, polycystic disease of the ovaries, pancreatic pseudocysts and ascites, leukemia, meningioma, cancerous cachexia, inhibition of H pylori, psoriasis, chronic rejection of allografts as well as Alzheimer's disease and finally osteoporosis.

7. Use according to claim 6, characterized in that the pathological states or diseases to be treated are chosen from the group comprising the following pathological states or  
25 diseases: acromegalia, hypophyseal adenomas or endocrinic gastroenteropancreatic tumors including carcinoid syndrome, and gastrointestinal bleeding.